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Publication Title:

5-MEMBERED HETEROCYCLES FOR THE TREATMENT OF HUMAN DISEASES INVOLVING MODULATORS OF SELECTINS

Abstract:

Abstract of WO0033836

Compounds of formulas (1), (2) and (3) are disclosed, where at least one and no more than two of R<1>, R<2>, R<3>, R<4> or R<5> are as defined in Group 1. In said formulas R<1> is typically a moiety containing a terminal carboxylic acid group such as phenoxy acetic acid, R<2> is typically a hydrophobic moiety such as functionalized alkyl chain or a functionalized aryl group, and R<3> is typically a functionalized aryl group, and they are within the scope of this invention. These compounds exhibit inhibitory activity against the Selectins and are indicated in the treatment of human diseases involving Selectins. Data supplied from the esp@cenet database - Worldwide

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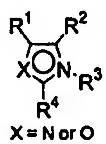

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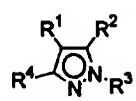

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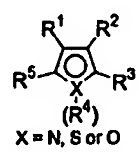

(3)

(57) Abstract

Compounds of formulas (1), (2) and (3) are disclosed, where at least one and no more than two of R^1, R^2, R^3, R^4 or R^5 are as defined in Group 1. In said formulas R^1 is typically a moiety containing a terminal carboxylic acid group such as phenoxy acetic acid, R^2 is typically a hydrophobic moiety such as functionalized alkyl chain or a functionalized aryl group, and R^3 is typically a functionalized aryl group, and they are within the scope of this invention. These compounds exhibit inhibitory activity against the Selectins and are indicated in the treatment of human diseases involving Selectins.

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5-membered Heterocycles for the Treatment of Human Diseases Involving Modulators of Selectins

This application claims the benefit of the filing date of provisional application serial no. 60/111,026, filed on December 4th 1998, and provisional application serial no. 60/111,025 filed on December 4th 1998, the disclosure of which is incorporated herein by reference.

Field of the Invention

The present invention relates to novel selectin modulating compounds having the structural **Formulas 1, 2** and **3**, as shown below, to methods of their preparation, to compositions comprising the compounds, to their use for treating human or animal disorders, to their use for purification of proteins, and to their use for in diagnostics. These compounds are modulators of selectin (P-, E- and L-selectin) Ligand (e.g. Sialyl Lewis X (sLe^X)) interactions for the management, treatment, control, or as an adjunct of diseases in humans caused by selectins. More particularly, this invention relates to the administration of compounds according to **Formulas 1**, **2** and **3** which are selectin/Ligand antagonists, for the management of diseases and disease states such as 1) acute respiratory distress syndrome (ARDS), 2) diseases that may be controlled *via* inhibition of angiogenesis, 3) asthma, 4) atherosclerosis, 5) atopic dermatitis, contact dermatitis, and cutaneous inflammation, 6) bowel inflammation, 7) diabetes/diabetes-associated pathologies, 8) Grave's disease and associates conditions, 9) multiple sclerosis (MS), 10) myocardial ischemia/reperfusion injury, 11) organ transplantation,

12) psoriasis, 13) rheumatoid arthritis, 14) stroke and ischemic brain trauma, 15) trauma-induced organ injury, 16) thrombosis, 17) reduction of tumor metastasis and/or tumor growth, and the like.

Background of the Invention

The immune response relies on the ability of specialized immune cells--leukocytes and lymphocytes--to migrate to sites of tissue damage, infection, or other insult to the body. Once there, these cells mount a defense against the intruding organism, help to repair the injured tissue, and protect the body from further damage. The immune system is also in constant "surveillance mode". Circulating lymphocytes monitor the body for pathogens by migrating through lymphoid tissues, where they can be exposed to antigens and become activated.

In order for these processes to occur, various chemoattractants, cytokines, and cell adhesion molecules (CAMs) act in a programmed, sequential manner to form what has been termed the leukocyte-endothelial cascade (Tedder *et al.*, *FASEB* 9: 866 (1995), Albelda *et al.*, *FASEB* 8:1756, (1994)). Three known families of CAMs participate in this cascade: the selectins, the integrins and the immunoglobulin superfamily. The first step, rolling of leukocytes and lymphocytes along the blood vessel wall, is mediated by the selectins.

Selectins are a small family of transmembrane glycoproteins that bind to cell surface carbohydrate ligands (for reviews see: Lasky, Science 258: 964 (1992); McEver, *Curr. Opin. Immun.* 6: 75 (1994); McEver, *J. Biol. Chem.* 270:

11025 (1995)). To date, three members have been identified: P-selectin (expressed on platelets and vascular endothelial cells, L-selectin (on leukocytes), and E-selectin (on vascular endothelial cells). Common structural features include a calcium-dependent (C-type) lectin domain, an epidermal growth factor (EGF)-like domain, and a series of short consensus 'complement regulatory protein' repeat sequences. Rodent homologs have been cloned and they share a high degree of sequence homology with their human counterparts.

Several selectin counter-receptors have been identified (for review see: Lasky et al., in *Cellular Adhesion: Molecular Definition to Therapeutic Potential*, Metcalf *et al.*, Eds. pp.37-53 (1994) and the like). L-selectin binds to at least three different ligands: Glycam-1, CD34 and MAdCAM-1, each being expressed on different tissues. P-selectin has been found to bind to PSGL-1, and E-selectin has been found to bind to ESL-1. These cell-surface selectin ligands are capped with clusters of oligosaccharides (for discussion see: Rosen *et al.*, *Curr. Opin. Cell Biol.* 6: 663 (1994), and Bertozzi *et al.*, *Chemistry. & Biology* 2: 703 (1995)). The specific carbohydrate moieties necessary for selectin binding have been identified: the sialylated and fucosylated tetrasaccharide sialyl Lewis X (sLe^{x}), and a related structure sialyl Lewis a (sLe^{a}), are common motifs recognized by all three selectins.

Although leukocyte recruitment into the tissue is a normal, indeed essential, component of the immune response, excessive and uncontrolled recruitment results in inflammatory disease. As adherence of immune cells to vascular endothelium is a critical event in the pathogenesis of acute inflammation, modulation of selectin function is indicated in the management of diseases and disease states as described below.

Selectin function can be modulated by altering cell-surface expression, by competitive inhibition, or by shedding/cleavage from the cell surface (Diaz-Gonzalez, *et al.*, *J. Clin. Invest.* 95: 1756 (1995); Whelan, *Trends Biochem. Sci.* 21 (1996)). While they have been identified as inhibitors of selectin-ligand interactions *in vitro*, compounds of **Formulas 1**, **2** and **3** may reduce inflammation *in vivo via* any or all of these modes.

Accordingly, the compounds of the present invention, which exhibit inhibitory activity against the selectins, are indicated in the treatment or management of the foregoing diseases (references supporting each indication are noted):

1) acute respiratory distress syndrome (ARDS) (Carraway *et al.*, *Am. J. Respir. Crit. Care Med.* 157: 938 (1998); Moss *et al.*, *Crit. Care Med.* 24: 1782 (1996) and others);
2) diseases that may be controlled *via* inhibition of angiogenesis (Koch *et al*, *Nature* 376: 517-519 (1995); Detmar *et al.*, *J. Invest. Dermatol.* 111:1 (1998); Nguyen *et al*, *Nature* 365: 267-269 (1993));
3) asthma (Gundal *et al.*, *J. Clin. Invest.* 88: 1407 (1991); DeSanctis *et al.*, *J. Appl. Physiol.* 83: 681, (1997); Kogan *et al.*, *J. Med. Chem.* 41: 1099 (1998); *PRNewswire*, Sept. 9, 1998);
4) atherosclerosis (Dong *et al.*, *J. Clin. Invest.* 102: 145 (1998); Frijns *et al.*, *Stroke* 28: 2214 (1997); Tenaglia *et al.*, *Am. J. Cardiol.* 79: 742 (1997); Zeitler *et al.*, *Eur. J. Med. Res.* 2: 389 (1997), and others);
5) atopic dermatitis, contact dermatitis, and cutaneous inflammation (Teixeira and Hellewell, *J. Immunol.* 161: 2516 (1998); Staite *et al.*, *Blood* 88: 2973

(1996); Todderud *et al., J. Pharmacol. Exp. Therap.* 282: 1298 (1997); Ohnishi *et al., Immunopharmacol.* 34: 161 (1996), and the like);

6) bowel inflammation (Schurmann *et al.*, Gut 36: 411 (1995); Koizumi *et al., Gastroenterology* 103: 840 (1992); Bhatti *et al., Gut* 43: 40 (1998); Cellier *et al., Eur. J. Gastroenterol. Hepatol.* 9: 1197 (1997));

7) diabetes/diabetes-associated pathologies (Kunt *et al., Exp. Clin. Endocrinol. Diabetes* 106: 183 (1998); Kopp *et al., Exp. Clin. Endocrinol. Diabetes* 106: 41 (1998); Albertini *et al., Diabetes Care* 21: 1008 (1998); Bannan *et al., Diabetologica* 41: 460 (1998), and others);

8) Grave's disease and associates conditions (Hara *et al., Endocr. J.* 43:709 (1996); Pappa *et al., Clin Exp. Immunol.* 108: 309 (1997); (Miyazaki *et al., Clin. Exp. Immunol.* 89: 52 (1992); Aubert *et al., Clin. Immunol. Immunopathol.* 76: 170 (1995), and the like);

9) multiple sclerosis (MS) (McDonnell *et al., J. Neuroimmunol.* 85: 186 (1998)); Washington *et al., Ann. Neurol.* 35: 89 (1994); Vora *et al., Mult. Scler.* 3: 171 (1997); Archelos *et al., J. Neurol. Sci.* 159: 127 (1998));

10) myocardial ischemia/reperfusion injury (reviewed in Lefer, *Ann Thorac Surg. 60*: 773-777 (1995), also Yamada *et al., Eur. J. Pharmacol.* 346: 217 (1998), Kilgore *et al., J. Pharmacol. Exp. Ther.* 284: 427 (1998); Lefer *et al., Circulation* 90: 2390 (1994));

11) organ transplantation (Naka *et al., Proc. Natl. Acad. Sci.* 94: 757 (1997); Andreassen *et al., Am. J. Cardiol.* 81: 604 (1998); Koo *et al. Am. J. Pathol.* 153: 557 (1998); Dulkanchainun *et al., Ann. Surg.* 227: 832 (1998); Takada *et al., Transplantation* 64: 1520 (1997); Brandt *et al., Eur. J. Cardiothorac. Surg.* 12: 781 (1997); Garcia-Criado *et al., J. Surg. Res.* 70: 187 (1997));

12) psoriasis (Veale *et al., Br. J. Dermatol.* 132: 32 (1995); Bonifati *et al., Dermatol.* 190: 128 (1995); Danno *et al., J. Dermatol. Sci.* 13: 49 (1996));

13) rheumatoid arthritis (Veale and Maple, *Drugs Aging* 9: 87 (1996); Hersmann *et al, Cell Adhesion Comm.* 6: 69 (1998); Walter and Issekutz, *Eur. J. Immunol.* 27: 1498 (1997); Ertenli *et al., J. Rheumatol.* 25: 1054 (1998) and others);

14) stroke and ischemic brain trauma (Suzuki *et al., Neurosci. Lett.* 13: 151 (1997); Connolly *et al., Circ. Res.* 81: 304 (1997); Morikawa *et al, Stroke* 27: 951 (1996));

15) trauma-induced organ injury (Simons *et al.*, J. *Trauma* 41: 653 (1996), Cocks *et al., J. Trauma* 45: 1 (1998); Mulligan *et al., Nature* 359: 843 (1994); Rubio-Avilla *et al., J. Trauma* 43: 313 (1997) and others);

16) thrombosis (Minamino *et al., J. Clin. Invest.* 101: 1643 (1998); (Downing *et al., J. Vasc. Surg.* 25: 816 (1997) and the like);

17) reduction of tumor metastasis and/or tumor growth (Hebbar *et al., Proc. Amer. Assoc. Cancer Res.* 39:501, (1998); Khatib *et al., Proc. Amer. Assoc. Cancer Res.* 39:501, (1998); Kim et al., *Proc. Natl. Acad. Sci. USA.* 95: 9325-9330 (1998); El-Hariry *et al., Exp. Opin. Invest. Drugs* 6: 1465-1478 (1997), and others).

Comparison with other Selectin-Ligand Inhibitors/Antagonists

Sialyl-Lewis^X analogs/mimetics reported in the literature include: 'GSC-150' (Kanebo) which has been reported to have IC_{50} values of 280 μM, 100 μM, and 30 μM against E-, P-, L-selectin respectively when assayed using an ELISA assay (Tsujishita *et al., J. Med. Chem.* 40: 362 (1997)); TBC-1269 (Texas Biotech) which has been reported to have IC_{50}

values of 500 μM, 70 μM, and 560 μM against E-, P-, and L-selectin respectively, when assayed using a cell adhesion assay (Kogan *et al.*, *J. Med. Chem.* 41: 1099 (1998)); a macrocyclic derivative, which has an IC_{50} of 390 μM against E-selectin (Kolb, *Bioorg. Med. Chem. Lett.* 7: 2629 (1997)); and C-mannose derivatives which have IC_{50} values of 100-160 μM against E-selectin (Marron *et al.*, *Tet. Lett.* 37: 9037 (1996)). Some of the most potent derivatives that have been reported are multivalent sialyl-Lewis^X analogs which have IC_{50} values of ~1 nM in an L-selectin cell adhesion assay (Renkonen *et al.*, *Glycobiology* 7: 453 (1997)).

Some additional sugar based inhibitors of interest include inositol hexakisphosphate (IP-6) and sulfated galactocerebrosides ("sulfatides"). IP-6 has been reported to have IC_{50} values of 160 μM and 2 μM, against P- and L-selectin respectively, in competition ELISA assays (Cecconi *et al.*, *J. Biol. Chem.* 21: 15060 (1994)). Sulfatides have IC_{50} values in the 0.1-12 μM range when tested in a P-selectin competition ELISA assay (Marinier *et al.*, *J. Med. Chem.* 40: 3234 (1997)). BMS-190394, a sulfatide analog, has been reported to have IC_{50} values of 18 μM and 10 μM, in P-, and L-selectin cell adhesion assays respectively (Todderud *et al.*, *J. Pharmacol. Exp. Therap.* 282: 1298 (1997)). Mannose-containing natural products showed inhibition of P-selectin with an IC_{50} value of 60 μM (Ikeda *et al.*, *Bioorg. Med. Chem. Lett.* 7: 2485 (1997)).

Non-carbohydrate inhibitors include peptides based on a conserved region of the lectin domain of the selectins, which have activity in P- and E-selectin cell adhesion assays with IC_{50} values of ~20 μM (Briggs *et al.*, *Glycobiology* 5: 583 (1995)). Additional peptides, discovered by random

screening, have IC_{50} values of 5-10 μM in an E-selectin cell adhesion assay (Martens *et al.*, *J. Biol. Chem.* 270: 21129 (1995)).

Summary of the Invention

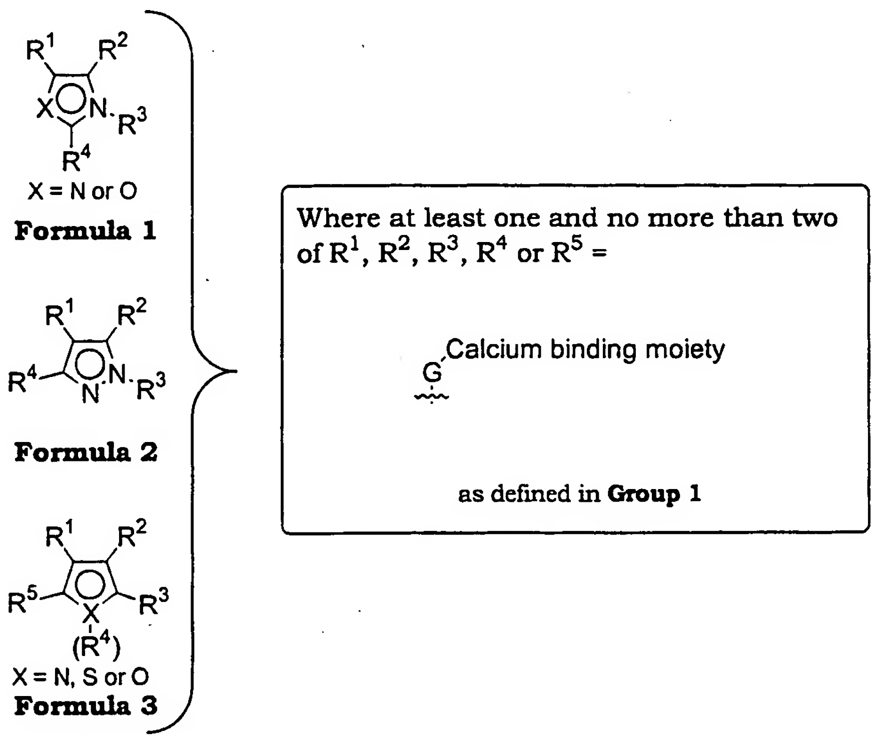
The present invention is based on the discovery that compounds of **Formulas 1**, **2** and **3** are inhibitors or modulators of selectins which render them particularly useful for the treatment or management of a large number of disease states in which the role of selectins has directly or indirectly been implicated.

It has been found that the requisite selectin modulating activity can be obtained by employing a planar, rigid, five-membered ring template which acts as a scaffold, to which one can attach the necessary appendages that are required for activity. In order to obtain the desired selectin modulating activity the appendant groups that must be attached to the central template are 1) a carboxylic acid moiety as defined in Group I, or carboxylic acid isostere; or other calcium binding moiety which will be apparent to those skilled in the art; and 2) a hydrophobic moiety such as a $C_{12}H_{25}$ alkyl chain. Additional substitution about the central core is necessary to modify the potency, selectivity and physiological properties, of the compounds claimed herein. To this end, the compounds of the present invention include any derivative with a rigid core when substituted with a carboxylic acid moiety as defined in **Group I** or a carboxylic acid isostere; or other calcium binding moiety which will be apparent to those skilled in the art, and a hydrophobic moiety as defined herein.

Accordingly, an object of the present invention is to provide a method for inhibiting or modulating selectins in a mammal by the administration of compound according to **Formulas 1, 2** and **3**.

Another object of the present invention relates to pharmaceutical compositions containing an effective inhibiting amount of compound according to **Formulas 1, 2** and **3**.

These compounds have the following general structural **Formulas 1, 2** and **3**:



Formulas 1, 2 and 3

Definitions

As used herein, the term "attached" signifies a stable covalent bond, certain preferred points of attachment being apparent to those skilled in the

art.

The terms "halogen" or "halo" include fluorine, chlorine, bromine, and iodine.

The term "alkyl" includes C_1-C_{16} straight chain saturated, C_1-C_{16} branched saturated, C_3-C_8 cyclic saturated and C_1-C_{16} straight chain or branched saturated aliphatic hydrocarbon groups substituted with C_3-C_8 cyclic saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, this definition shall include but is not limited to methyl (Me), ethyl (Et), propyl (Pr), butyl (Bu), pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, isopropyl (i-Pr), isobutyl (i-Bu), *tert*-butyl (*t*-Bu), *sec*-butyl (s-Bu), isopentyl, neopentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopropylmethyl, and the like.

The term "alkenyl" includes C_2-C_{16} straight chain unsaturated, C_2-C_{11} branched unsaturated, C_5-C_8 unsaturated cyclic, and C_2-C_{16} straight chain or branched unsaturated aliphatic hydrocarbon groups substituted with C_3-C_8 cyclic saturated and unsaturated aliphatic hydrocarbon groups having the specified number of carbon atoms. Double bonds may occur in any stable point along the chain and the carbon-carbon double bonds may have either the cis or trans configuration. For example, this definition shall include but is not limited to ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, 1,5-octadienyl, 1,4,7-nonatrienyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, ethylcyclohexenyl, butenylcyclopentyl, 1-pentenyl-3-cyclohexenyl, and the like.

The term "alkyloxy" (e.g. methoxy, ethoxy, propyloxy, allyloxy, cyclohexyloxy) represents an alkyl group as defined above having the

indicated number of carbon atoms attached through an oxygen bridge.

The term "alkylthio" (e.g. methylthio, ethylthio, propylthio, cyclohexylthio and the like) represents an alkyl group as defined above having the indicated number of carbon atoms attached through a sulfur bridge.

The term "alkylamino" represents one or two alkyl groups as defined above having the indicated number of carbon atoms attached through an amine bridge. The two alkyl groups maybe taken together with the nitrogen to which they are attached forming a cyclic system containing 3 to 8 carbon atoms with or without one C_1-C_{16}alkyl, arylC_0-C_{16}alkyl, or C_0-C_{16}alkylaryl substituent.

The term "alkylaminoalkyl" represents an alkylamino group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term “alkyloxy(alkyl)amino” (e.g. methoxy(methyl)amine, ethoxy(propyl)amine) represents an alkyloxy group as defined above attached through an amino group, the amino group itself having an alkyl substituent.

The term "alkylcarbonyl" (e.g. cyclooctylcarbonyl, pentylcarbonyl, 3-hexylcarbonyl) represents an alkyl group as defined above having the indicated number of carbon atoms attached through a carbonyl group.

The term "alkylcarboxy" (e.g. heptylcarboxy, cyclopropylcarboxy, 3-pentenylcarboxy) represents an alkylcarbonyl group as defined above wherein the carbonyl is in turn attached through an oxygen.

The term "alkylcarboxyalkyl" represents an alkylcarboxy group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term "alkylcarbonylamino" (e.g. hexylcarbonylamino, cyclopentylcarbonyl-aminomethyl, methylcarbonylaminophenyl) represents an alkylcarbonyl group as defined above wherein the carbonyl is in turn attached through the nitrogen atom of an amino group. The nitrogen group may itself be substituted with an alkyl or aryl group.

The term "aryl" represents an unsubstituted, mono-, di- or trisubstituted monocyclic, polycyclic, biaryl and heterocyclic aromatic groups covalently attached at any ring position capable of forming a stable covalent bond, certain preferred points of attachment being apparent to those skilled in the art (e.g. 3-indolyl, 4-imidazolyl). The aryl substituents are independently selected from the group consisting of halo, nitro, cyano, trihalomethyl, C_{1-16}alkyl, arylC_{1-16}alkyl, C_{0-16}alkyloxyC_{0-16}alkyl, arylC_{0-16}alkyloxyC_{0-16}alkyl, C_{0-16}alkylthioC_{0-16}alkyl, arylC_{0-16}alkylthioC_{0-16}alkyl, C_{0-16}alkylaminoC_{0-16}alkyl, arylC_{0-16}alkylaminoC_{0-16}alkyl, di(arylC_{1-16}alkyl)aminoC_{0-16}alkyl, C_{1-16}alkylcarbonylC_{0-16}alkyl, arylC_{1-16}alkylcarbonylC_{0-16}alkyl, C_{1-16}alkylcarboxyC_{0-16}alkyl, arylC_{1-16}alkylcarboxyC_{0-16}alkyl, C_{1-16}alkylcarbonylaminoC_{0-16}alkyl, arylC_{1-16}alkylcarbonylaminoC_{0-16}alkyl, $-C_{0-16}$alkyl$COOR_1$, $-C_{0-16}$alkyl$CONR_2R_3$ wherein R_1, R_2 and R_3 are independently selected from hydrogen, C_1-C_{11}alkyl, arylC_0-C_{11}alkyl, or R_2 and R_3 are taken together with the nitrogen to which they are attached forming a cyclic system containing 3 to 8 carbon atoms with or without one C_1-C_{16}alkyl, arylC_0-C_{16}alkyl, or C_0-C_{16}alkylaryl substituent.

The definition of aryl includes but is not limited to phenyl, biphenyl, naphthyl, dihydronaphthyl, tetrahydronaphthyl, indenyl, indanyl, azulenyl, anthryl, phenanthryl, fluorenyl, pyrenyl, thienyl, benzothienyl,

isobenzothienyl, 2,3-dihydrobenzothienyl, furyl, pyranyl, benzofuranyl, isobenzofuranyl, 2,3-dihydrobenzofuranyl, pyrrolyl, indolyl, isoindolyl, indolizinyl, indazolyl, imidazolyl, benzimidazolyl, pyridyl, pyrazinyl, pyradazinyl, pyrimidinyl, triazinyl, quinolyl, isoquinolyl, 4H-quinolizinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, chromanyl, benzodioxolyl, piperonyl, purinyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, benzthiazolyl, oxazolyl, isoxazolyl, benzoxazolyl, oxadiazolyl, thiadiazolyl.

The term "arylalkyl" (e.g. (4-hydroxyphenyl)ethyl, (2-aminonaphthyl)hexyl, pyridylcyclopentyl) represents an aryl group as defined above attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term “carbonyloxy” represents a carbonyl group attached through an oxygen bridge.

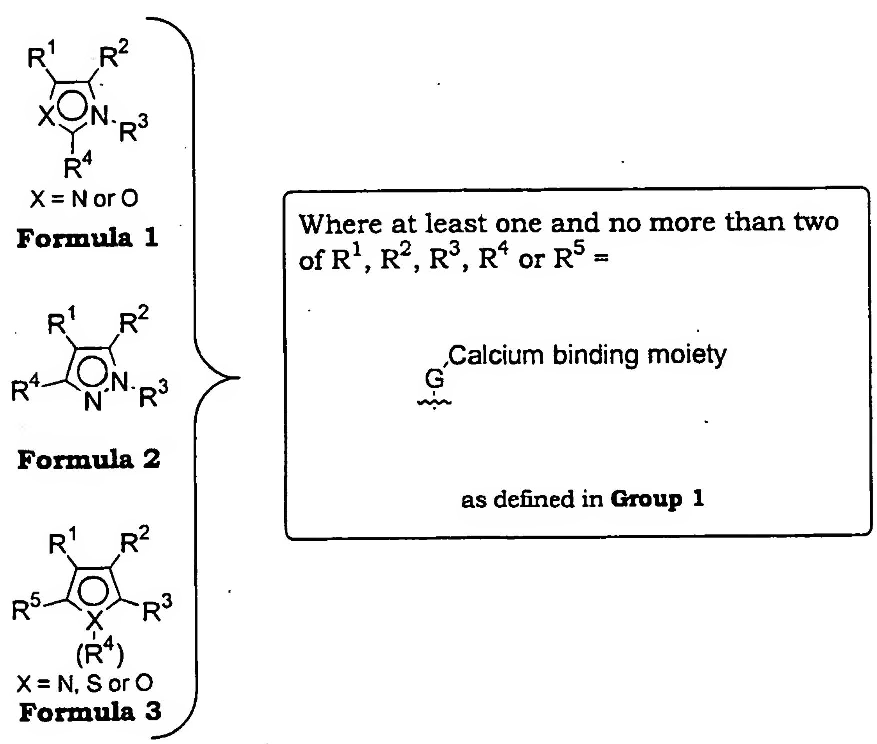
In the above definitions, the terms “alkyl” and “alkenyl” maybe used interchangeably in so far as a stable chemical entity is formed, as obvious to those skilled in the art.

The compounds of the present invention also includes racemic mixtures, stereoisomers and mixtures of said compounds, including isotopically-labeled and radio-labeled compounds (Goding; *Monoclonal Antibodies Principles and Practice*; Academic Press, p.104 (1986)). Such isomers can be isolated by standard resolution techniques, including fractional crystallization and chiral chromatography (Eliel, E. L. and Wilen S.H.; *Stereochemistry in Organic Compounds; John Wiley & Sons, New York,* (1993)).

The term "therapeutically effective amount" shall mean that amount of drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

Detailed Description

This application relates to compounds having the general **Formulas 1**, **2** and **3**. Accordingly, an object of the present invention is to provide a method for inhibiting or modulating selectins in a mammal by the administration of a compound according to the general **Formulas 1**, **2** and **3** as defined below. In addition, this application relates to the preparation of said compounds, to compositions comprising the compounds, to their use for treating human or animal disorders, to their use for purification of proteins, and to their use in diagnostics or medical devices.



Formulas 1, 2 and 3

The present invention relates to compounds having **General Formula 1**, **General Formula 2**, and **General Formula 3** wherein at least one and no

more than two of R^1, R^2, R^3 or R^4 must be selected from **Group I**. The following substitution patterns are possible for the remaining R groups:

Case A: When one of R^1, R^2, R^3, R^4, or *R^5 (*in General Formula 3) is selected from **Group I** (templates **1-6**), one of R^1, R^2, R^3, R^4 or *R^5 must be selected from **Group II**, one of R^1, R^2, R^3, R^4 and *R^5 must be selected from **Group III** and one of R^1, R^2, R^3, R^4 and *R^5 must be selected from **Group IV**. The remaining R group must be either unsubstituted or be equal to Hydrogen; where **Groups I, II, III** and **IV** are defined below;

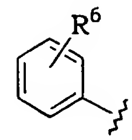
Case B: When two of R^1, R^2, R^3, R^4,or *R^5 (*in General Formula 3) are selected from **Group I** (templates **1-6**), one of R^1, R^2, R^3, R^4 or *R^5 must be selected from **Group II**, and one of R^1, R^2, R^3, R^4 or *R^5 must be selected from **Group IV**. The remaining R groups must be either unsubstituted or be equal to Hydrogen; where **Groups I, II, III** and **IV** are defined below;

Case C: When one of R^1, R^2, R^3, R^4, or *R^5 (*in General Formula 3) is selected from **Group I** (template **7**), one of R^1, R^2, R^3, R^4 or *R^5 must be selected from **Group V**, and one of R^1, R^2, R^3, R^4 or *R^5 must be selected from **Group VI**. The remaining R groups must be either unsubstituted or be equal to Hydrogen; where **Groups I, II, III** and **IV** are defined below;

Case D: When two of R^1, R^2, R^3, R^4, or *R^5 (*in General Formula 3) are selected from **Group I** (template **7**), one of R^1, R^2, R^3, R^4 or *R^5 must be selected from **Group V**. The remaining R groups must be either unsubstituted or be equal to Hydrogen; where **Groups I, V,** and **VI** are defined below;

Definitions of Group I through Group IV

Group I is defined in Figure 1, Table 1, below:

Group I = 

where R^6 equals one of the following in Table 2:

Figure 1

Table 1

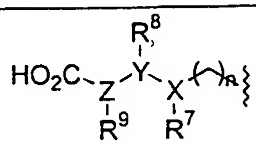
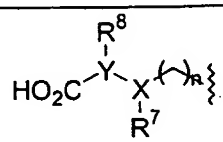
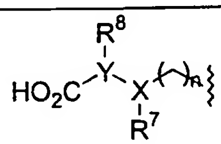
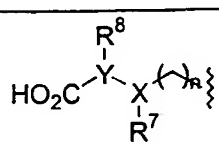
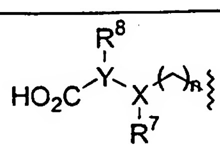
R^6 Type	**Template**	**Atom or group**					
		X	**Y**	**Z**	**R^7**	**R^8**	**R^9**
i	 **1**	C	N	CH	=O	H	$(CH_2)_{n'}OH$
ii	 **2a**	CH	$(CH_2)_{n'}$	-	$(CH_2)_{n''}CO_2H$	-	-
iii	 **2b**	N	C	-	H	=O	-
iv	 **2c**	CH	CH	-	-OH	- OH	-
v	 **2d**	N	$(CH_2)_{n'}$	-	-H	-	-

Table 1(cont.)

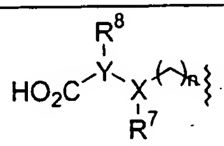
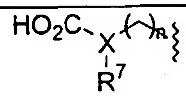
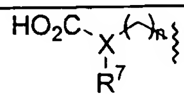
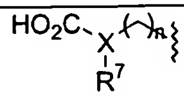
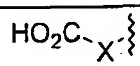
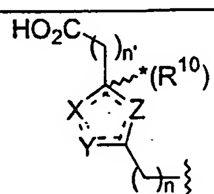
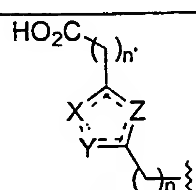
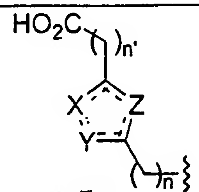
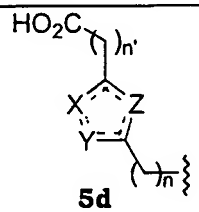
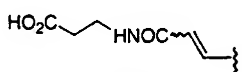
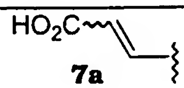
R6 Type	Template	Atom or group					
		X	**Y**	**Z**	**R^7**	**R^8**	**R^9**
vi	 **2e**	O	$(CH_2)_{n'}$	-	-	-	-
vii	 **3a**	C	-	-	=O	-	-
viii	 **3b**	CH	-	-	-OH	-	-
ix	 **3c**	CH	-	-	$-NH_2$	-	-
x	 **4a**	$(CH_2)_{n'}$	-	-	-	-	-
xi	 **5a**	O	N	CH *(no R^{10}) or CH_2 *(R^{10}=H)	-	-	-
xii	 **5b**	S, O or NH	CH	N	-	-	-

Table 1(cont.)

R^6 Type	Template	Atom or group					
		X	Y	Z	R^7	R^8	R^9
xiii	 5c	N	CH	S, O, or NH	-	-	-
xiv	 5d	CH	S, O, or NH	N	-	-	-
xv	 6a	-	-	-	-	-	-
xvi	 7a	-	-	-	-	-	-

(n", and/or n' and/or n can be 0, 1, 2, 3, 4, 5 or 6)

Group II is defined as one of the following:

(i) $C_{0-6}CO_2R^{11}$, $C_{0-6}CONHR^{11}$, $C_{0-6}NHCOR^{11}$, $C_{0-6}NHC(O)NHR^{11}$, $C_{0-6}NHSO_2R^{11}$, wherein R^{11} is C_{8-16} alkyl, or C_{3-8} alkylaryl, in which the said aryl group such as phenyl, thienyl, imidazoyl, indolyl, furyl or pyridyl, is mono- or disubstituted with a member selected from the group consisting of hydrogen, hydroxy, halo, C_{1-6} alkyl and C_{1-6} alkyloxy, C_{1-6} cycloalkyloxy, or C_1-C_4 alkyl aryl or C_1-C_4 alkoxy aryl, in which said aryl group is either unsubstituted, mono- or

disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-4} alkyl, or C_{1-4} alkyloxy; or

(ii) substituted or unsubstituted C_{8-16} alkyl or substituted C_{8-16} alkenyl, wherein the substituents are selected from the group consisting of hydrogen, hydroxy, C_{1-6} alkyloxy, amino, C_{1-6} alkylamino, or C_{1-6} dialkylamino, or aryl; or

(iii) Unsubstituted, mono-, di-, or tri-substituted aryl-C_{0-11} alkyl wherein aryl is selected from the group consisting of phenyl, or pyridino, wherein the substituents are selected from the group consisting of:

(a) $C_{0-6}CO_2R^{12}$, $C_{0-6}CON(*H)R^{12}$, $C_{0-6}NHSO_2R^{12}$, *trans*-$CH{=}CHCO_2R^{12}$, *trans*-$CH{=}CHCON(*H)R^{12}$, or cyclopropyl$CON(*H)R^{12}$ wherein R^{12} is C_{8-16} alkyl, bis-C_{4-16} alkyl (* no H), *N*-(methyl) C_{8-16} alkyl (* no H), C_{8-16} alkyloxyalkyl, C_{0-3} alkyl C_{7-10} perfluoroalkyl, C_{5-8} cycloalkyl, C_{2-11} alkylaryl, C_{1-5} alkylaryl C_{1-8} alkyl, aminoaryl, C_{0-4} alkyltetrahydrofurfuryl, C_{0-4} alkyldiphenylmethyl which the said alkyl group or said aryl group such as phenyl, thienyl, imidazoyl, C or N-linked indolyl, furyl, benzotriazole, or pyridyl, are unsubstituted, mono- or disubstituted with a member selected from the group consisting of hydroxy, carboxy, halo, C_{1-6} alkyl and C_{1-6} alkyloxy, C_{1-6} cycloalkyloxy, C_1-C_4 alkyl aryl or C_1-C_4 alkoxy aryl, in which said aryl group is either unsubstituted, mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-4} alkyl, or C_{1-4} alkyloxy; or R^{10} can be N-Boc-piperidino, or N-carboethoxypiperidino;

Group III is defined as either:

(i) Hydrogen; or

(ii) Unsubstituted, mono or disubstituted C_{1-16} alkyl, C_{0-16} alkylamino, amino C_{0-16} alkyl, C_{0-6} alkylcarboxyl or C_{0-6} alkyl carboxyl ester, C_{0-16} alkyloxyalkyl or C_{2-16} alkenyl wherein the substituents are independently selected from the group consisting of hydroxy, C_{1-8} alkyl, C_{1-8} alkyloxyalkyl, C_{1-8} alkylthioalkyl, phenyl-C_{1-8} alkylamino, C_{1-8} alkoxycarbonyl; or C_{0-6} carboxyl, triazole, 2,3-(methylenedioxy)benzyl; or

(iii) substituted or unsubstituted N or C-linked pyrrolidino, piperidino, piperidonyl, morpholino, piperazino, N-Boc-piperazino, N-C_{1-10} alkylpiperazino, N-C_{3-6} alkenylpiperazino, N-(C_{1-6} alkoxy C_{1-6} alkyl)piperazino, N-(C_{1-6} alkoxy C_{3-6} alkenyl)piperazino, N-(C_{1-6} alkylamino C_{1-6} alkyl)piperazino, N-(C_{1-6} alkylamino C_{3-6} alkenyl)piperazino, uracil or other purine or pyrimidine heterocycles, wherein the substituents are N or C-linked as will be apparent to one skilled in the art, and are independently selected from:

(a) substituted C_{1-16} alkyloxy, C_{3-16} alkenyloxy, substituted C_{3-16} alkynyloxy; or

(b) substituted C_{1-6} alkyl-amino, di(substituted C_{1-6} alkyl)amino; or

(c) $CONHC_1$-C_{16} alkyl, $COOC_1$-C_{16} alkyl, C_{0-11} alkylCO_2H, $C_{0-11}NHC(O)NHR^{11}$, $C_{0-11}NHSO_2R^{11}$, *trans*- $CH{=}CHCO_2R^{11}$, or *trans*- $CH{=}CHCONHR^{11}$ wherein R^{11} is hydrogen, C_{1-16} alkyl, or C_{1-16} alkyl aryl, in which the said aryl group such as phenyl, or pyridyl, is mono- or disubstituted with a member

selected from the group consisting of hydroxy, halo, C_{1-6} alkyl and C_{1-6} alkyloxy, C_{1-6} cycloalkyloxy, or C_1-C_4 alkyl aryl or C_1-C_4 alkoxy aryl in which said aryl group is either unsubstituted, mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-4} alkyl, C_{1-4} alkyloxy, and aryl; or

(iv) either unsubstituted, mono-, di, or tri-substituted aryl, or C_0-C_{12} aryl such as phenyl, imidazolyl, furanoyl, pyrimidino, pyridino, or N or C-linked pyrrole or imidazolyl, wherein the substituents are independently selected from;

(a) hydroxy, halo; or

(b) unsubstituted or substituted C_{0-3} alkyloxy C_{0-3} alkyl, C_{3-16} alkenyloxy, substituted C_{3-16} alkynyloxy, aryl such as phenyl; or

(c) mono or di-substituted C_{1-6} alkyl-amino, di(substituted C_{1-6} alkyl)amino; or

(d) $CONHC_1$-C_{16} alkyl, $COOC_1$-C_{16} alkyl, C_{0-11} alkylCO_2H, $C_{0-11}NHC(O)NHR^{11}$, $C_{0-11}NHSO_2R^{11}$, *trans*- $CH{=}CHCO_2R^{11}$, or *trans*- $CH{=}CHCONHR^{11}$ wherein R^{11} is hydrogen, C_{1-16} alkyl, or C_{1-16} alkyl aryl, in which the said aryl group such as phenyl, or pyridyl, is mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-6} alkyl and C_{1-6} alkyloxy, C_{1-6} cycloalkyloxy, or C_1-C_4 alkyl aryl or C_1-C_4 alkoxy aryl in which said aryl group is either unsubstituted, mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-4}

alkyl, C_{1-4} alkyloxy, and aryl.

(e) O- or C-linked hexose or furanose such as mannose or fucose.

Group IV is defined as either:

(i)hydrogen; or

(ii)substituted or unsubstituted C_{1-16} alkyl or C_{2-12} alkenyl wherein the substituents are independently selected from the group consisting of hydroxy, C_{1-6} alkyloxy, C_{1-6}alkylthio, C_{1-6} alkylamino, phenyl-C_{1-6} alkylamino, C_{1-6} alkoxycarbonyl; or

(iv) mono, di or tri-substituted aryl C_{0-4} alkyl or substituted C_{0-4} alkyl aryl, wherein the aryl group is selected from phenyl, imidazolyl, indolyl, furyl, thienyl or pyridyl in which the substituents are selected from:

(a)hydrogen; or

(b)hydroxy or halo

Group V is defined as one of the following:

(i) Unsubstituted, mono-, di-, or tri-substituted aryl-C_{0-11} alkyl wherein aryl is selected from the group consisting of phenyl, or pyridino, wherein the substituents are selected from the group consisting of:

(a) $C_{0-6}CO_2R^{12}$, $C_{0-6}CON(*H)R^{12}$, $C_{0-6}NHSO_2R^{12}$, *trans*-$CH{=}CHCO_2R^{12}$, *trans*-$CH{=}CHCON(*H)R^{12}$, or cyclopropyl$CON(*H)R^{12}$ wherein R^{12} is C_{8-16} alkyl, bis-C_{4-16} alkyl (* no H), *N*-(methyl) C_{8-16} alkyl (* no H), C_{8-16} alkyloxyalkyl, C_{0-3} alkyl C_{7-10} perfluoroalkyl, C_{5-8} cycloalkyl, C_{2-11}

alkylaryl, C_{1-5} alkylaryl C_{1-8} alkyl, aminoaryl, C_{0-4} alkyltetrahydrofurfuryl, C_{0-4} alkyldiphenylmethyl which the said alkyl group or said aryl group such as phenyl, thienyl, imidazoyl, C or N-linked indolyl, furyl, benzotriazole, or pyridyl, are unsubstituted, mono- or disubstituted with a member selected from the group consisting of hydroxy, carboxy, halo, C_{1-6} alkyl and C_{1-6} alkyloxy, C_{1-6} cycloalkyloxy, C_1-C_4 alkyl.

Group VI is defined as one of the following:

(i) Hydrogen; or

(ii) either unsubstituted, mono-, di, or tri-substituted aryl, or C_0-C_{12} aryl such as phenyl, imidazolyl, furanoyl, pyrimidino, pyridino, or N or C-linked pyrrole or imidazolyl, wherein the substituents are independently selected from;

(a) hydroxy, halo; or

(b) CONHC_1-C_{16} alkyl, CONHC_{1-2} bis- C_{2-4} alkyl, COOC_1-C_{16} alkyl, C_{0-11} alkylCO_2H, C_{0-11}NHC(O)NHR^{11}, C_{0-11}NHSO_2R^{11}, *trans*-CH=CHCO_2R^{11}, or *trans*- CH=CHCONHR^{11} wherein R^{11} is hydrogen, C_{1-16} alkyl, or C_{1-16} alkyl aryl, in which the said aryl groups such as phenyl, or pyridyl, or alkyl groups are mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-6} alkyl and C_{1-6} alkyloxy, C_{1-6} cycloalkyloxy, or C_1-C_4 alkyl aryl or C_1-C_4 alkoxy aryl in which said aryl group is either unsubstituted, mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-4} alkyl, C_{1-4} alkyloxy, and aryl.

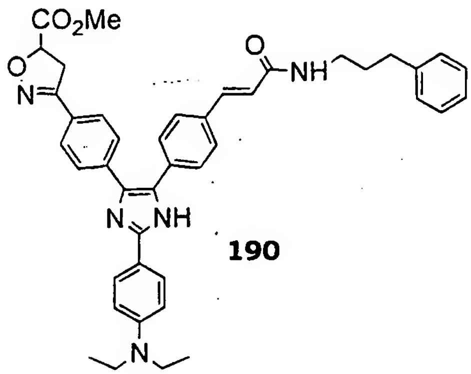
(c) O- or C-linked hexose or furanose such as mannose or fucose.

Detailed Description

The present invention related to compounds of the general formula A.

More particularly, the present invention relates to the compounds listed below in **Figure 2** or pharmaceutically acceptable salts or esters thereof:

Example 1



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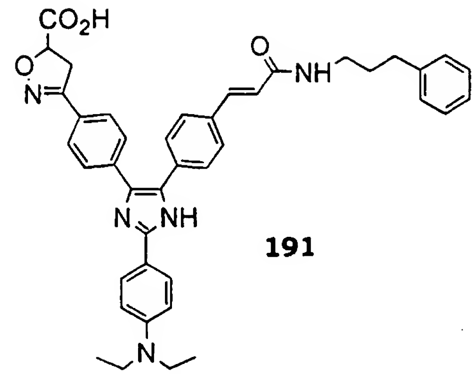
Example 2



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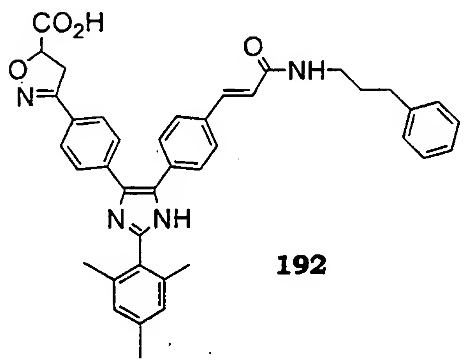
Example 3



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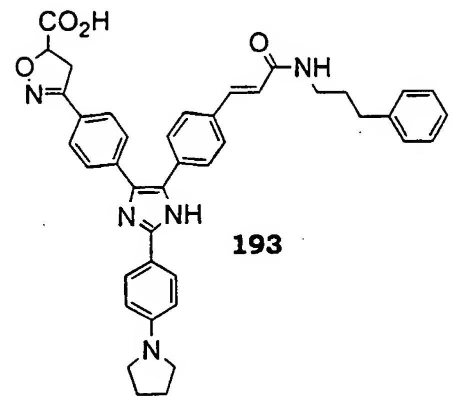
Example 4



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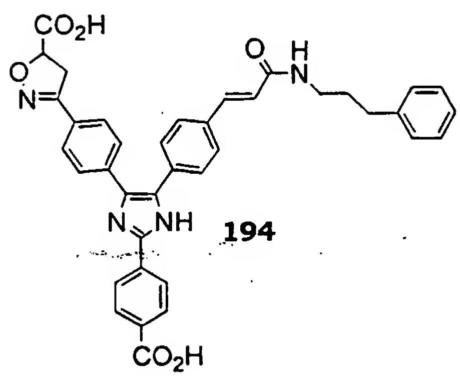
Example 5



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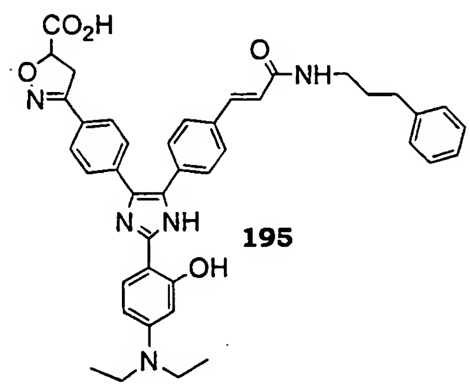
Example 6



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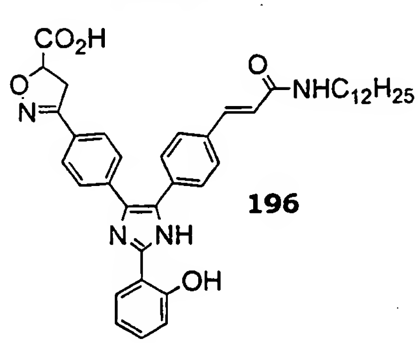
Example 7



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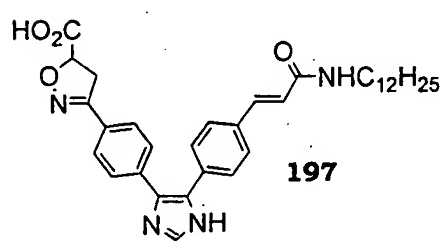
Example 8



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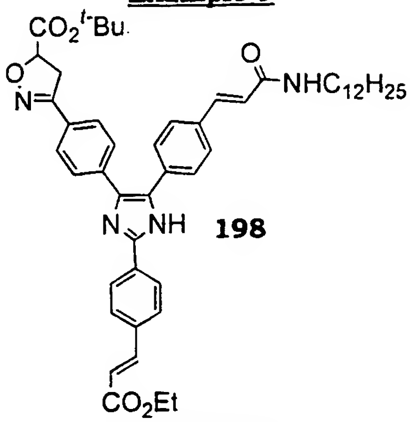
Figur

e 2

Example 9



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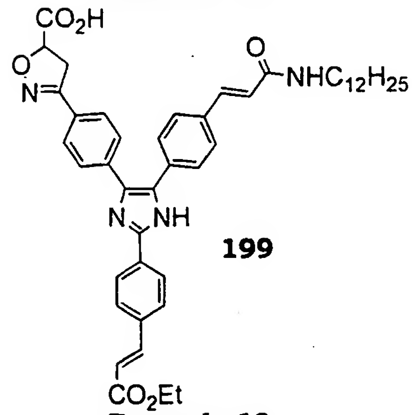
Example 10



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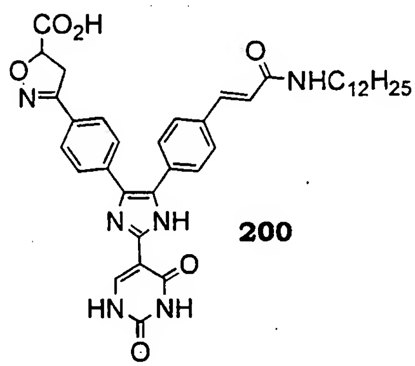
Example 11



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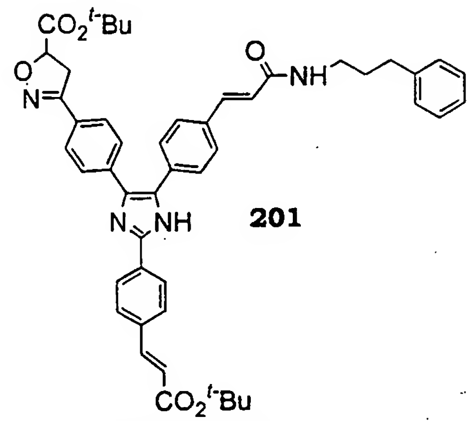
Example 12



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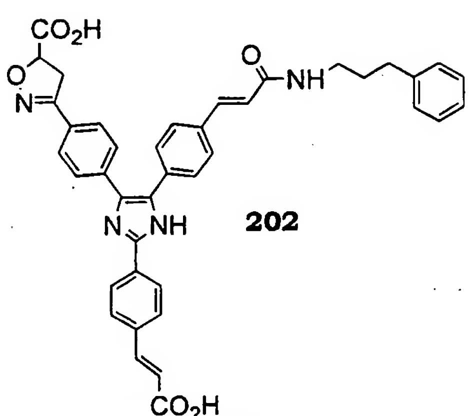
Example 13



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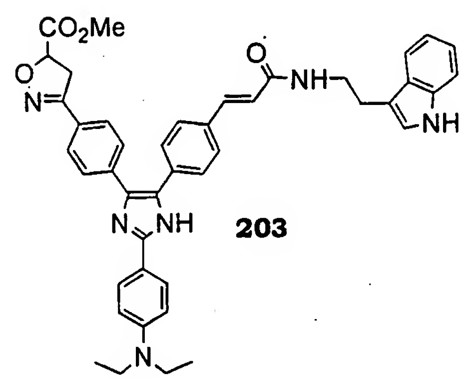
Example 14



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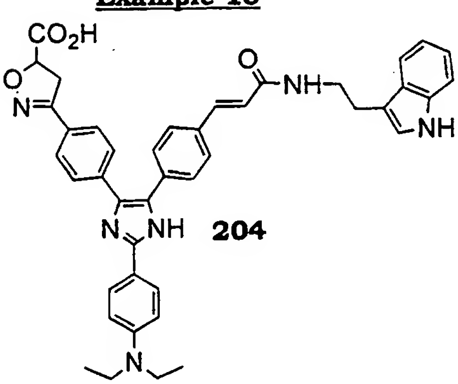
Example 15



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Example 16

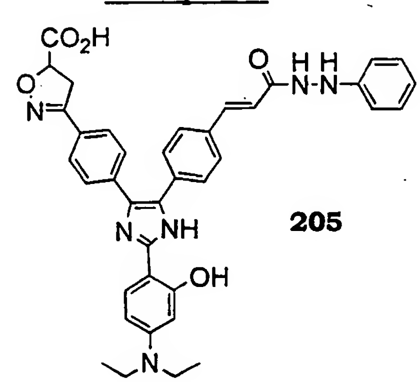

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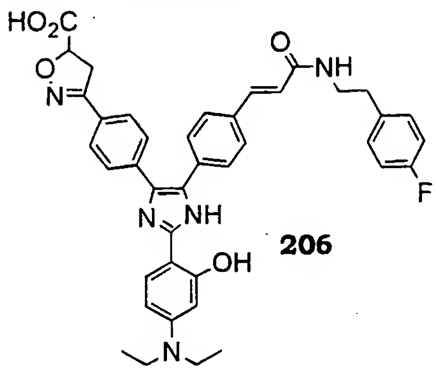
Figure 2 (cont.)

Example 17



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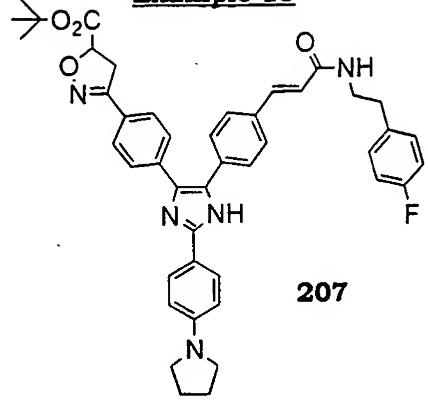
Example 18



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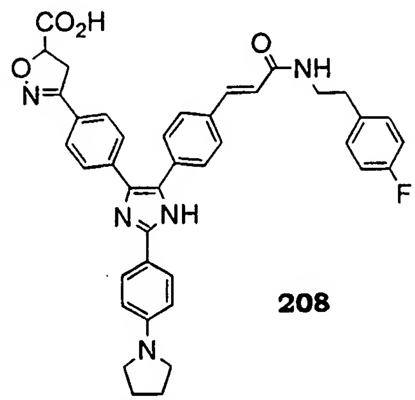
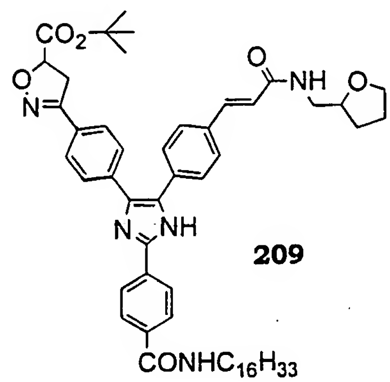
Example 19



208

Example 20



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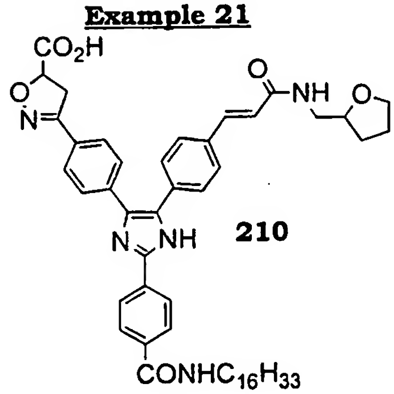
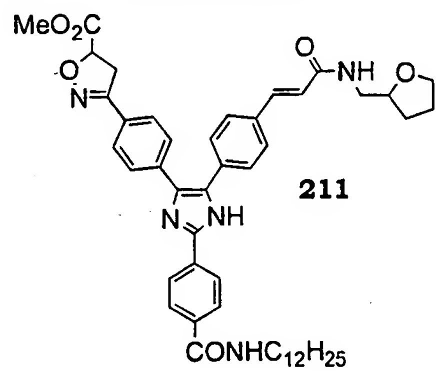
Example 21



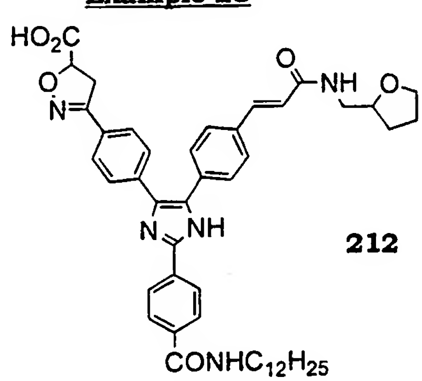
210

Example 22



211

Example 23



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Example 24

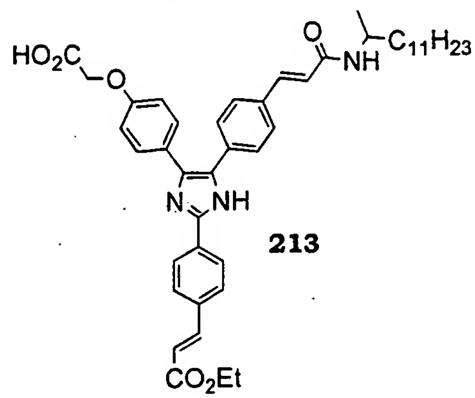

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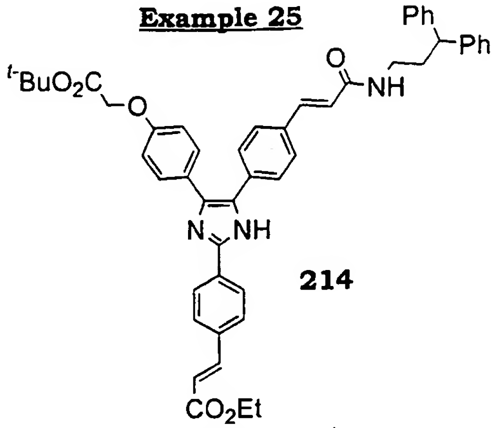
Figure 2 (cont.)

Example 25



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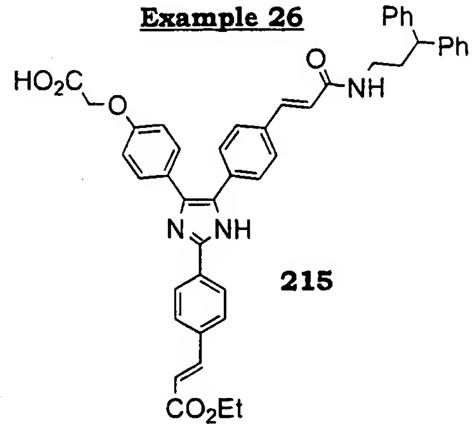
Example 26



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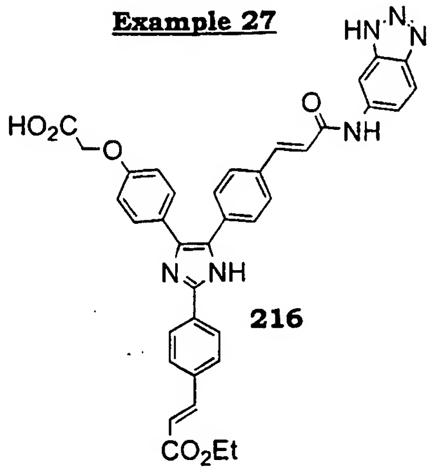
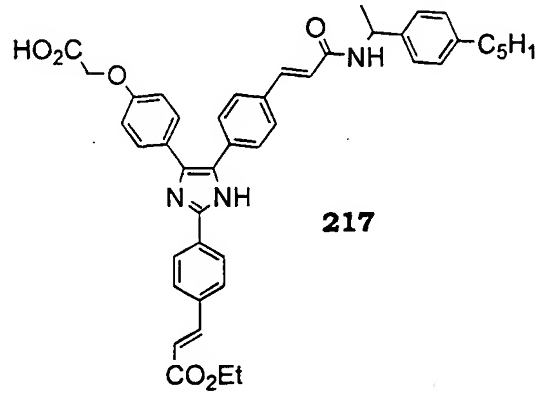
Example 27



216

Example 28



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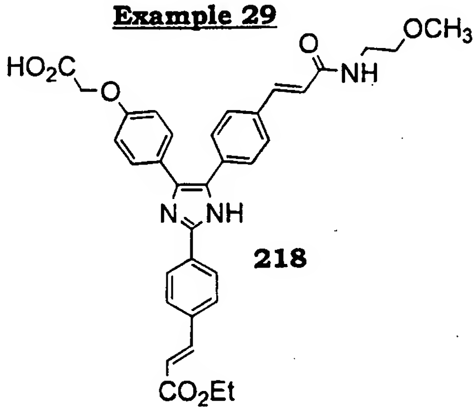
Example 29



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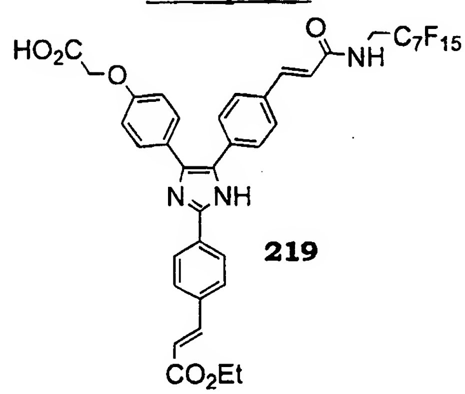
Example 30



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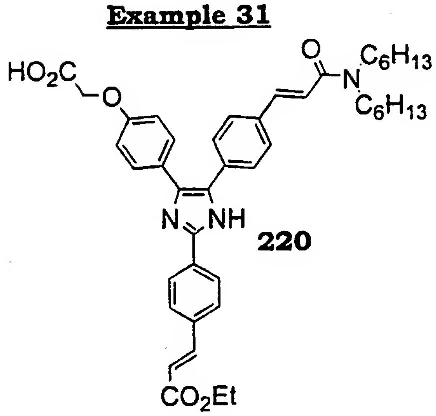
Example 31



220

Example 32

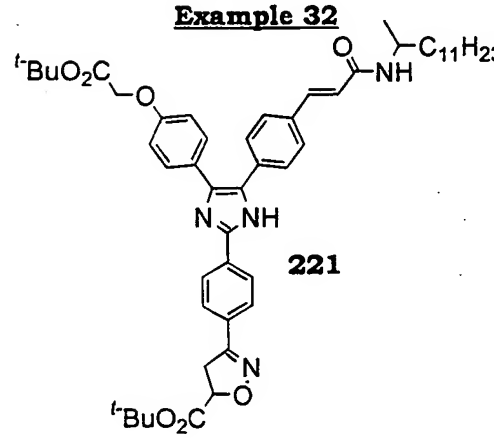


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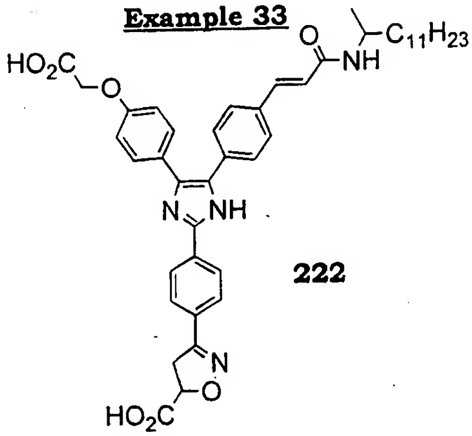
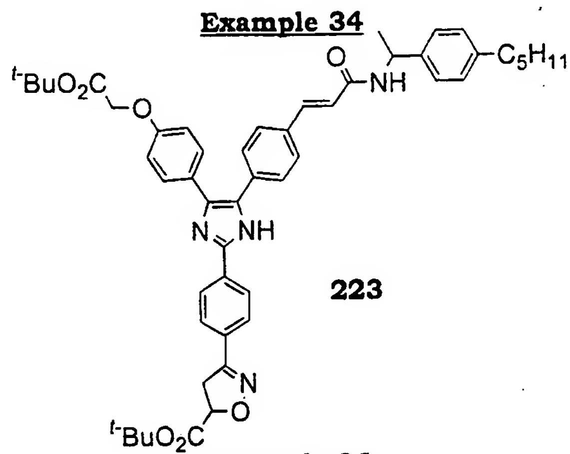
Figure 2 (cont.)

Example 33



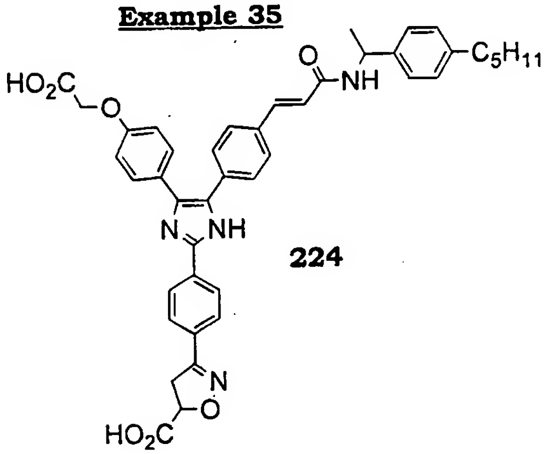
222

Example 34



223

Example 35



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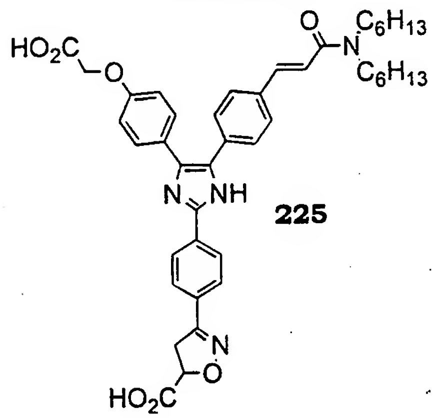
Example 36



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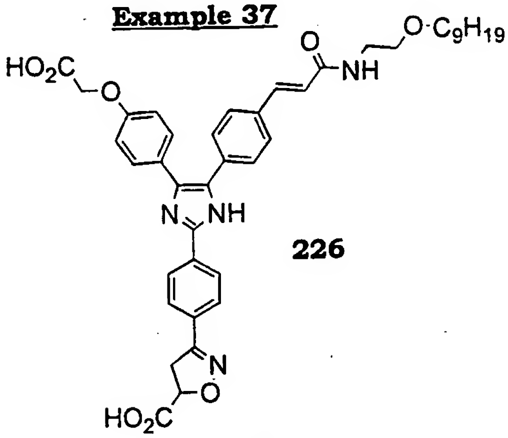
Example 37



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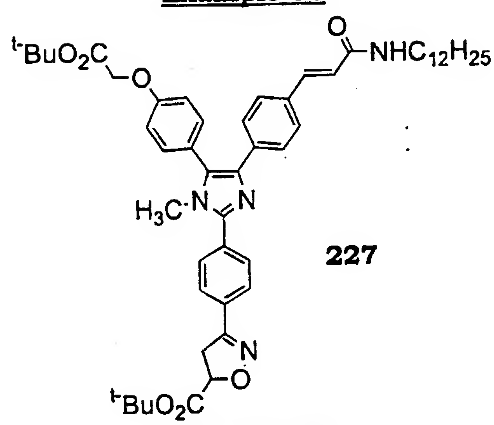
Example 38



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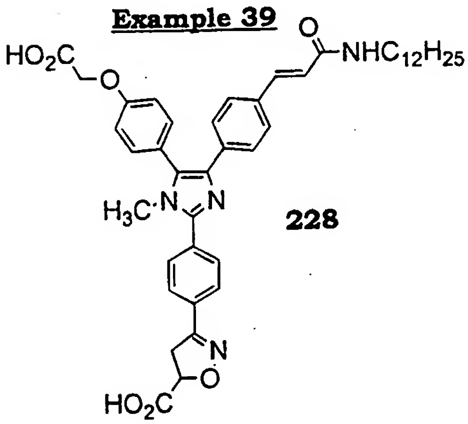
Example 39



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Example 40

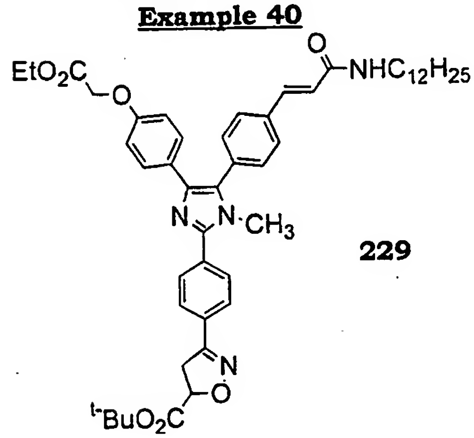

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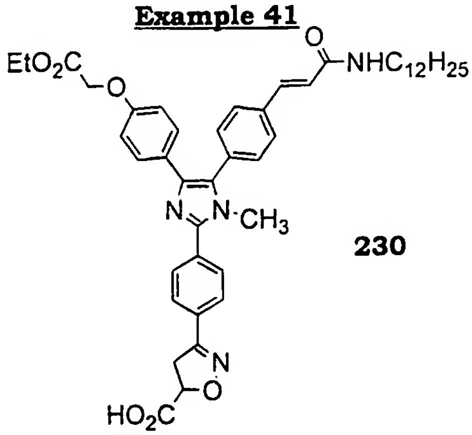
Figure 2 (cont.)

Example 41



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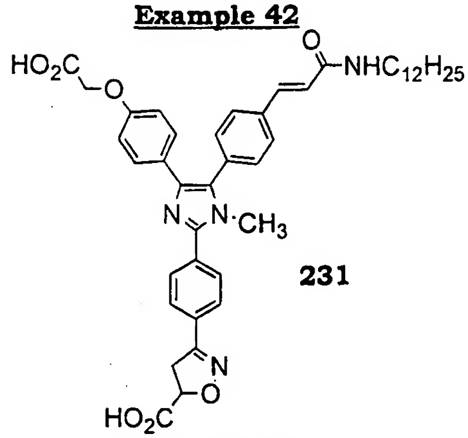
Example 42



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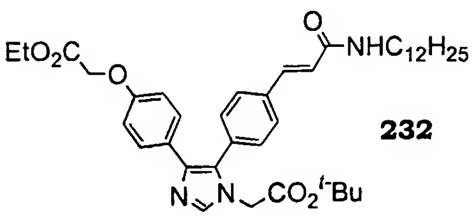
Example 43



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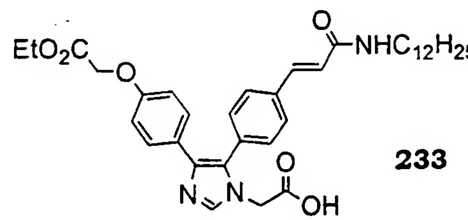
Example 44



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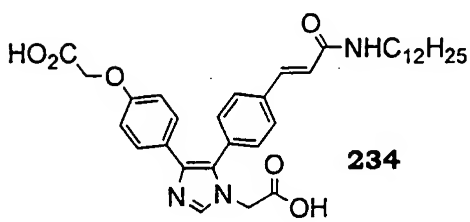
Example 45



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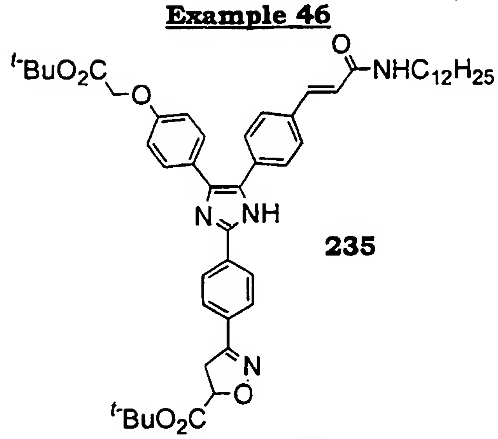
Example 46



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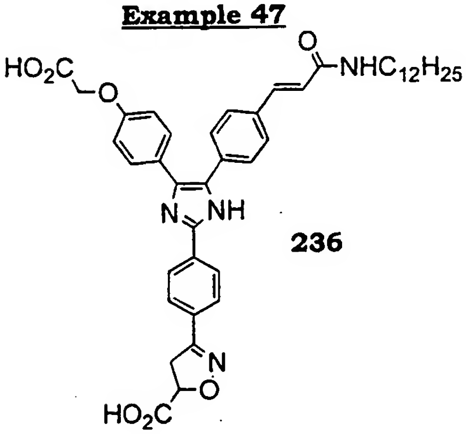
Example 47



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Example 48

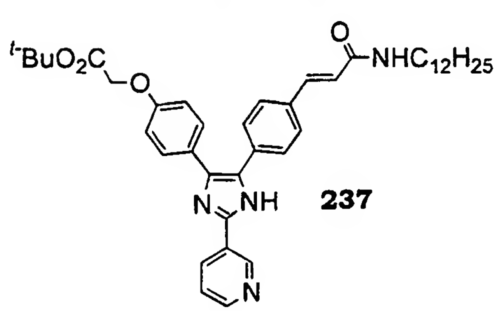

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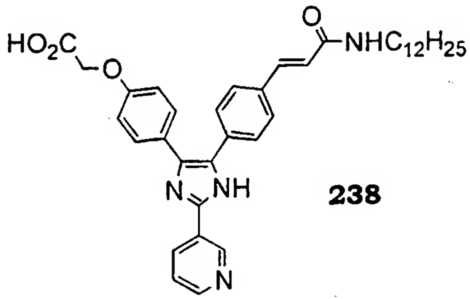
Figure 2 (cont.)

Example 49



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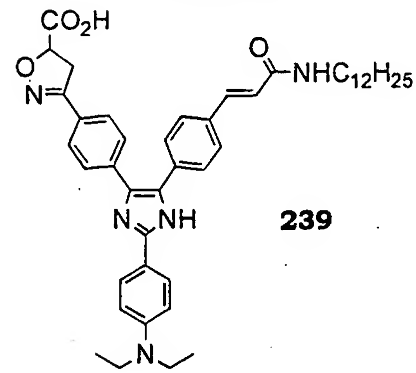
Example 50



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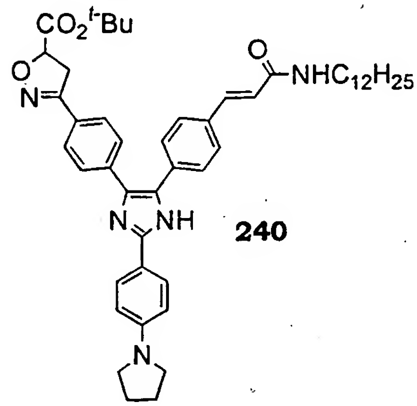
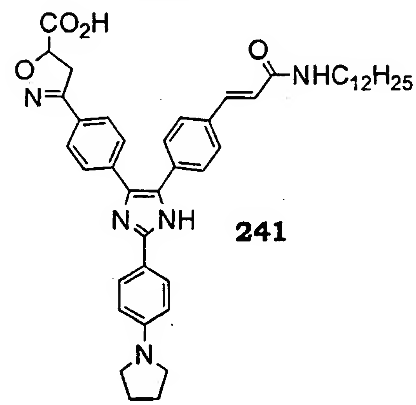
Example 51



240

Example 52



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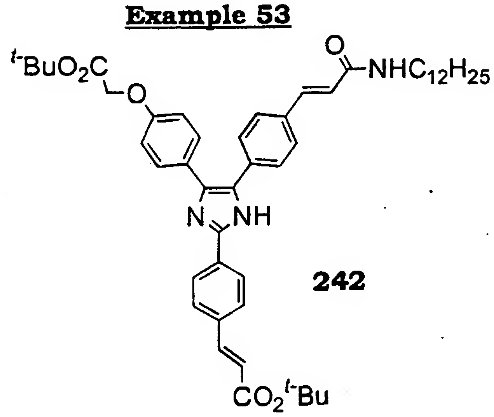
Example 53



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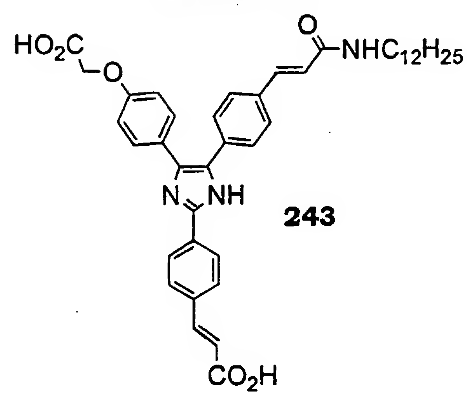
Example 54



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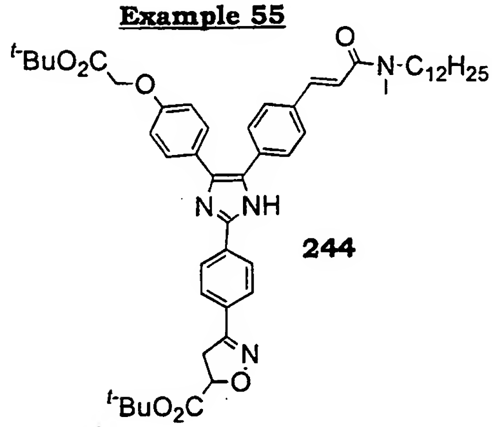
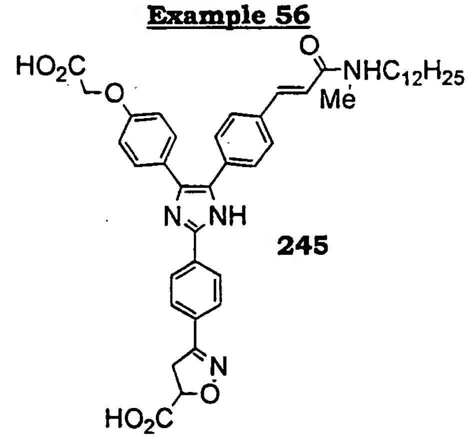
Example 55



244

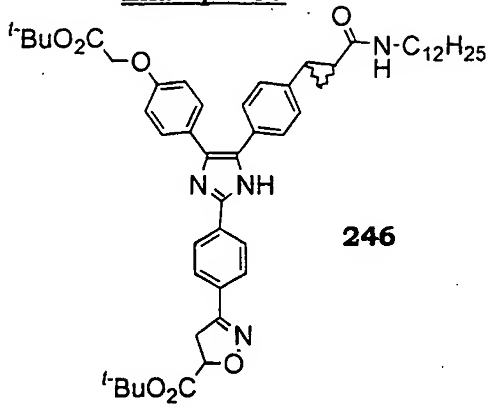
Example 56



245

Figure 2 (cont.)

Example 57



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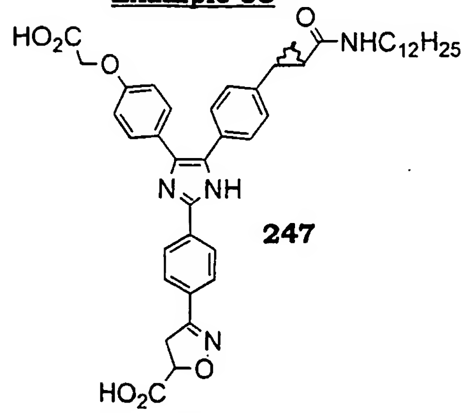
Example 58



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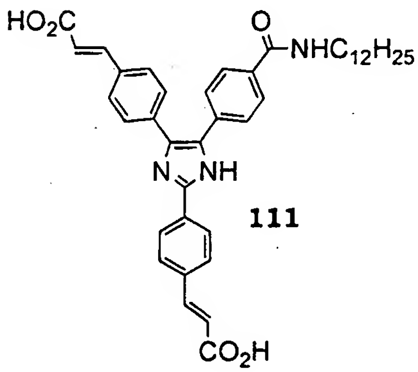
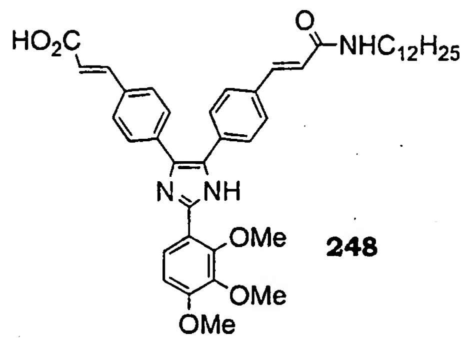
Example 59



111

Example 60



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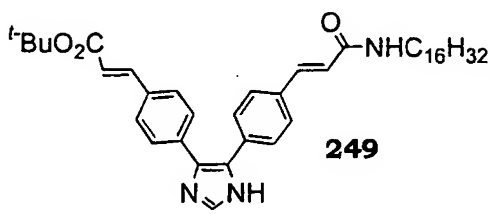
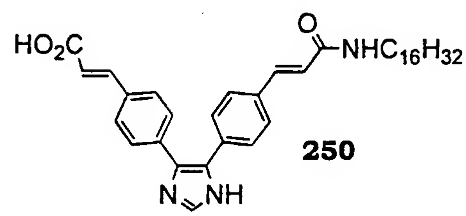
Example 61



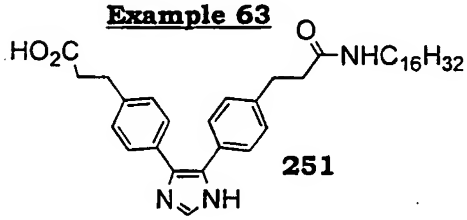
249

Example 62



250

Example 63



251

Example 64

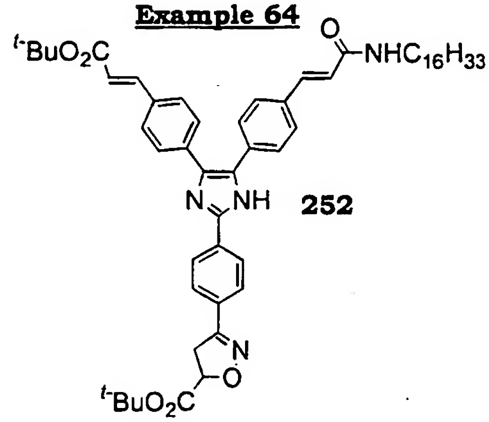


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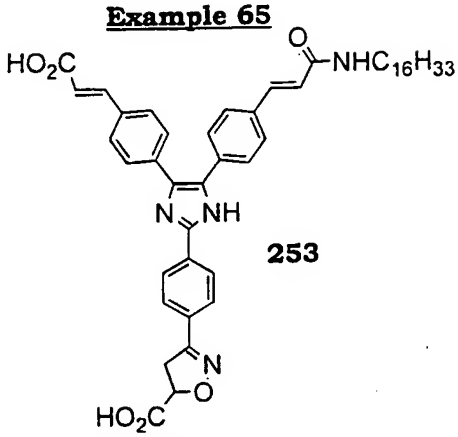
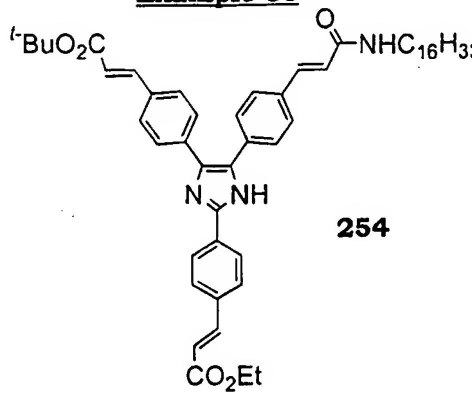
Figure 2 (cont.)

Example 65



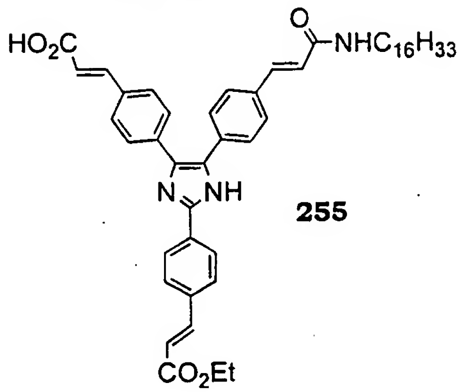
253

Example 66



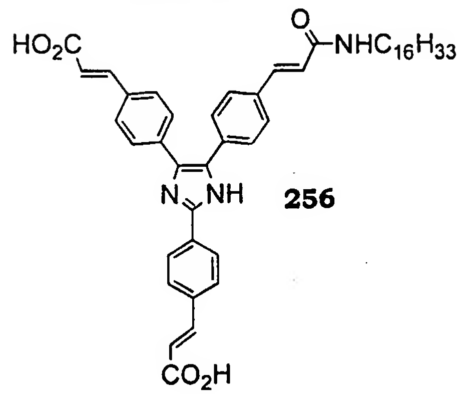
254

Example 67



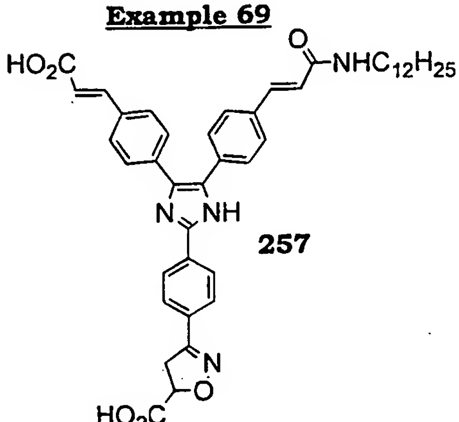
255

Example 68



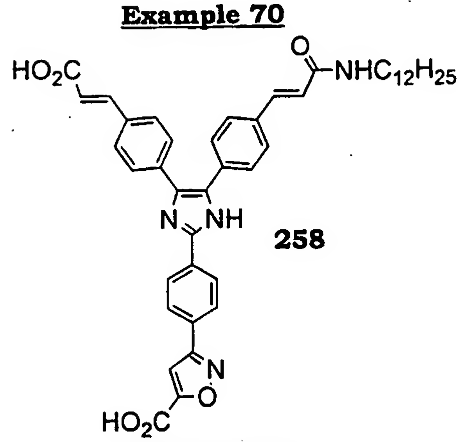
256

Example 69



257

Example 70



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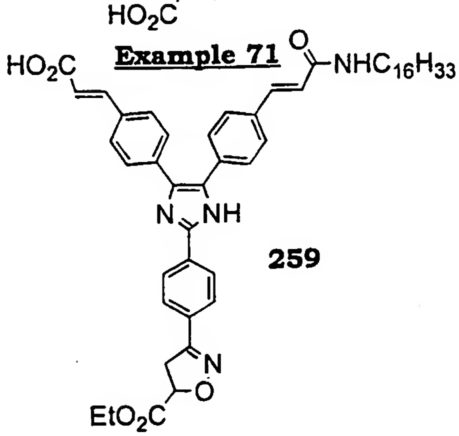
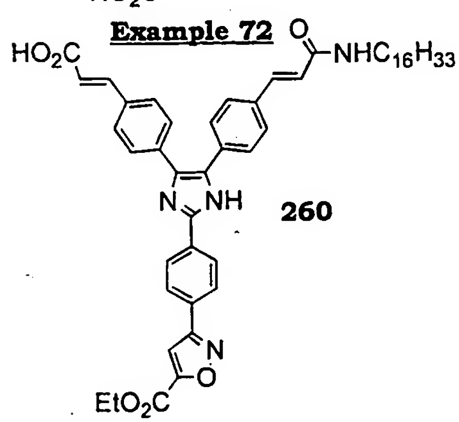
Example 71



259

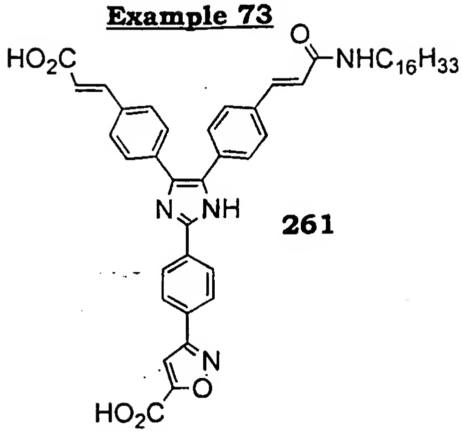
Example 72



260

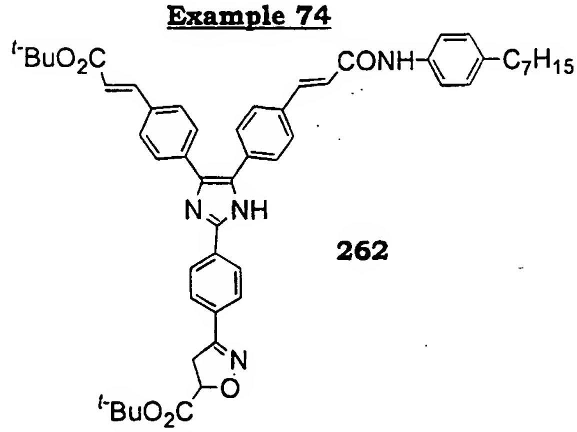
Figure 2 (cont.)

Example 73



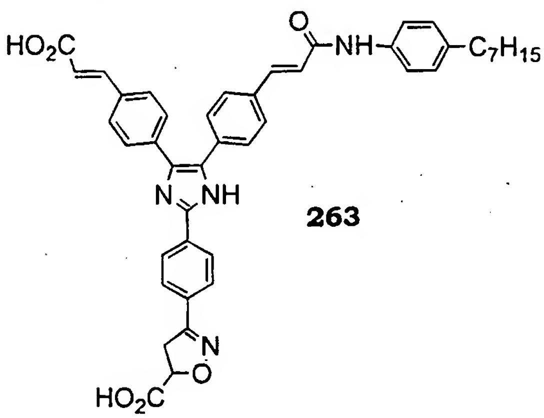
261

Example 74



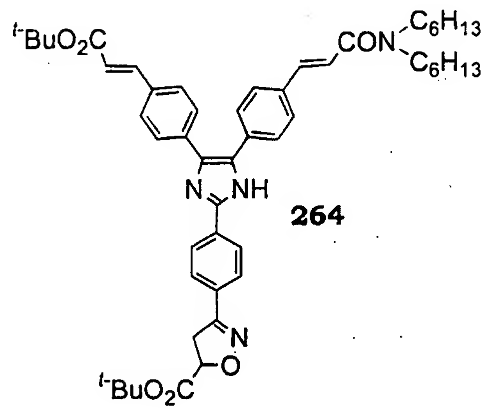
262

Example 75



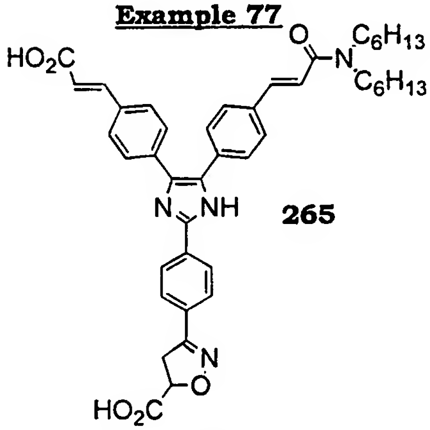
263

Example 76



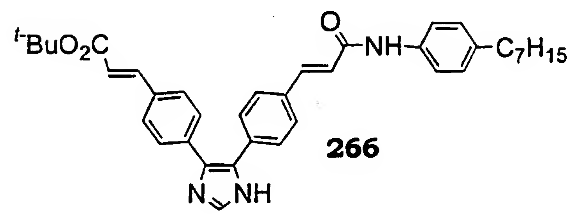
264

Example 77



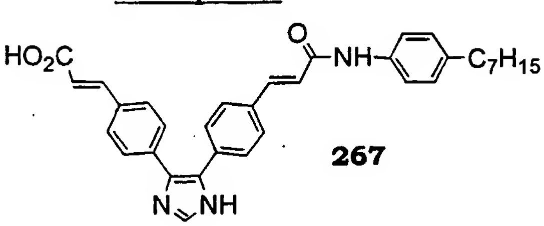
265

Example 78



266

Example 79



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Example 80

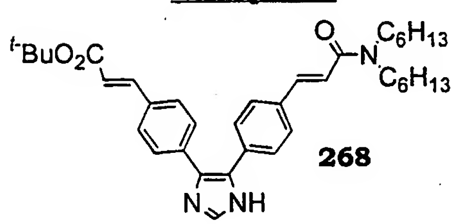

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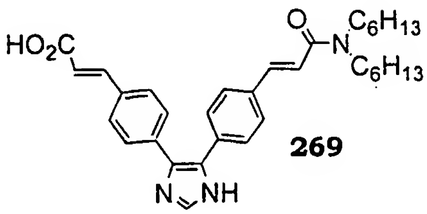
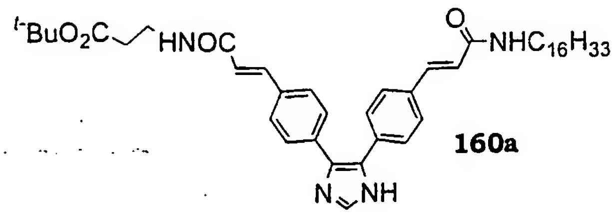
Figure 2 (cont.)

Example 81



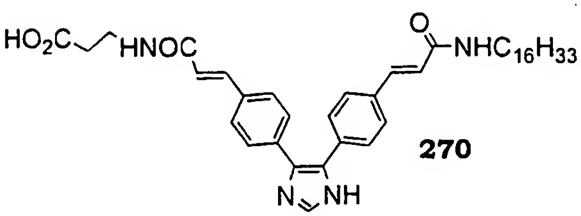
269

Example 82



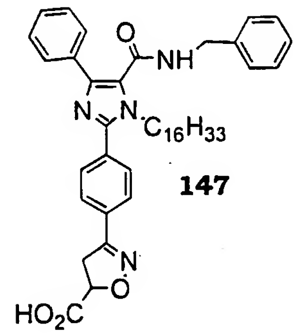
160a

Example 83



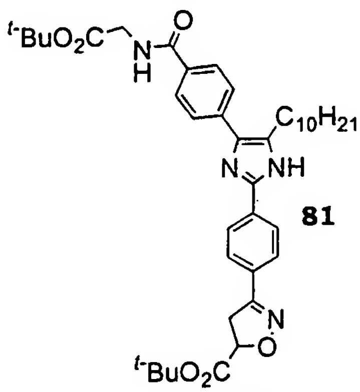
270

Example 84



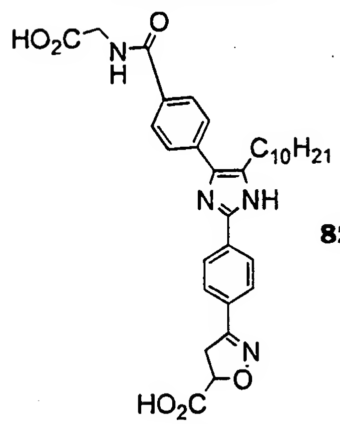
147

Example 85



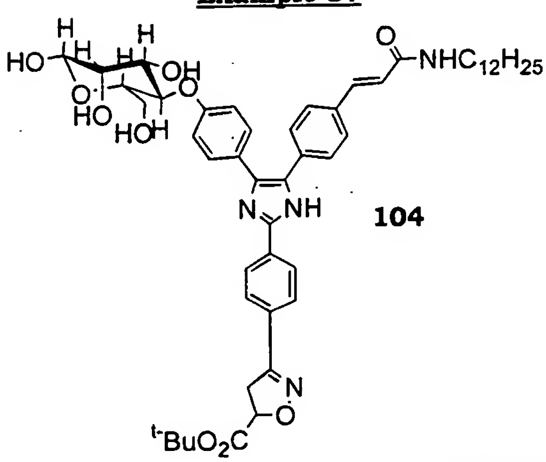
81

Example 86



82

Example 87



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Example 88

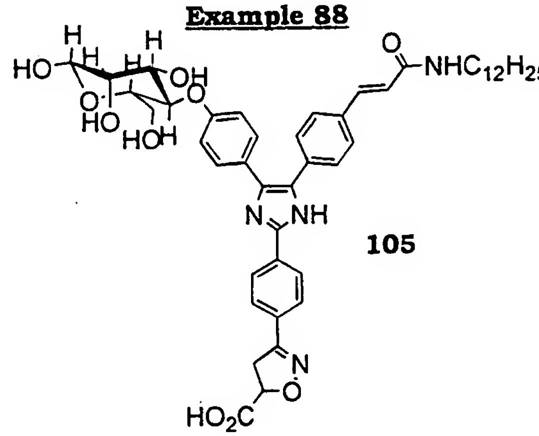

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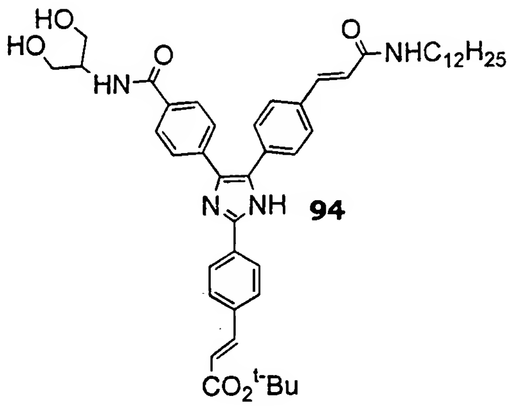
Figure 2 (cont.)

Example 89



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Example 90

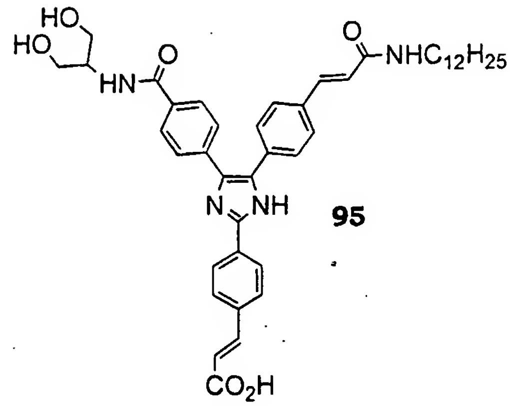

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Figure 2 (cont.)

The compounds depicted in **Figure 2** are named as follows:

Example 1

3-[4-(2-(4-Diethylamino-phenyl)-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester 190

Example 2

3-[4-(2-(4-Diethylamino-phenyl)-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid 191

Example 3

3-{4-[5-{4-[(E)-2-(3-Phenyl-propylcarbamoyl)-vinyl]-phenyl}-2-(2,4,6-trimethyl-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid 192

Example 4

3-{4-[5-{4-[(E)-2-(3-Phenyl-propylcarbamoyl)-vinyl]-phenyl}-2-(4-pyrrolidin-1-yl-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid 193

Example 5

3-[4-(2-(4-Carboxy-phenyl)-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid 194

Example 6

3-[4-(2-(4-Diethylamino-2-hydroxy-phenyl)-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid 195

Example 7

3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-(2-hydroxy-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid 196

Example 8

3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid 197

Example 9

3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 198

Example 10

3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid 199

Example 11

3-(4-{2-(2,4-Dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid 200

Example 12

3-[4-(2-[4-((E)-2-*tert*-Butoxycarbonyl-vinyl)-phenyl]-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 201

Example 13

3-[4-(2-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid 202

Example 14

3-{4-[2-(4-Diethylamino-phenyl)-5-(4-{(E)-2-[2-(1*H*-indol-3-yl)-ethylcarbamoyl]-vinyl}-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester 203

Example 15

3-{4-[2-(4-Diethylamino-phenyl)-5-(4-{(E)-2-[2-(1*H*-indol-3-yl)-ethylcarbamoyl]-vinyl}-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid 204

Example 16

3-[4-(2-(4-Diethylamino-2-hydroxy-phenyl)-5-{4-[(E)-2-(*N*-phenyl-hydrazinocarbonyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid 205

Example 17

3-{4-[2-(4-Diethylamino-2-hydroxy-phenyl)-5-(4-{(E)-2-[2-(4-fluoro-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid 206

Example 18

3-{4-[5-(4-{(E)-2-[2-(4-Fluoro-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-2-(4-pyrrolidin-1-yl-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 207

Example 19

3-{4-[5-(4-{(E)-2-[2-(4-Fluoro-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-2-(4-pyrrolidin-1-yl-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid 208

Example 20

<u>**3-{4-[2-(4-Hexadecylcarbamoyl-phenyl)-5-(4-{(E)-2-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-vinyl}-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester**</u> **209**

<u>Example 21</u>

<u>**3-{4-[2-(4-Hexadecylcarbamoyl-phenyl)-5-(4-{(E)-2-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-vinyl}-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid**</u> **210**

<u>Example 22</u>

<u>**3-{4-[2-(4-Dodecylcarbamoyl-phenyl)-5-(4-{(E)-2-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-vinyl}-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester**</u> **211**

<u>Example 23</u>

<u>**3-{4-[2-(4-Dodecylcarbamoyl-phenyl)-5-(4-{(E)-2-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-vinyl}-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid**</u> **212**

<u>Example 24</u>

<u>**[4-(2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-{4-[(E)-2-(1-methyl-dodecylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenoxy]-acetic acid**</u> **213**

<u>Example 25</u>

(4-{5-{4-[(E)-2-(3,3-Diphenyl-propylcarbamoyl)-vinyl]-phenyl}-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenoxy)-acetic acid *tert*-butyl ester 214

Example 26

(4-{5-{4-[(E)-2-(3,3-Diphenyl-propylcarbamoyl)-vinyl]-phenyl}-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenoxy)-acetic acid 215

Example 27

(4-{5-{4-[(E)-2-(3*H*-Benzotriazol-5-ylcarbamoyl)-vinyl]-phenyl}-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenoxy)-acetic acid 216

Example 28

{4-[2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-(4-{(E)-2-[1-(4-pentyl-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-1*H*-imidazol-4-yl]-phenoxy}-acetic acid 217

Example 29

[4-(2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-{4-[(E)-2-(2-methoxy-ethylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenoxy]-acetic acid 218

Example 30

[4-(2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-{4-[(E)-2-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluoro-octylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenoxy]-acetic acid 219

Example 31

(E)-3-(4-{4-(4-Carboxymethoxy-phenyl)-5-[4-((E)-2-dihexylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-acrylic acid ethyl ester 220

Example 32

3-[4-(4-(4-*tert*-Butoxycarbonylmethoxy-phenyl)-5-{4-[(E)-2-(1-methyl-dodecylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 221

Example 33

3-[4-(4-(4-Carboxymethoxy-phenyl)-5-{4-[(E)-2-(1-methyl-dodecylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid 222

Example 34

3-{4-[4-(4-*tert*-Butoxycarbonylmethoxy-phenyl)-5-(4-{(E)-2-[1-(4-pentyl-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-1*H*-imidazol-2-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 223

Example 35

3-{4-[4-(4-Carboxymethoxy-phenyl)-5-(4-{(E)-2-[1-(4-pentyl-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-1*H*-imidazol-2-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid 224

Example 36

3-(4-{4-(4-Carboxymethoxy-phenyl)-5-[4-((E)-2-dihexylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid 225

Example 37

3-[4-(4-(4-Carboxymethoxy-phenyl)-5-{4-[(E)-2-(2-nonyloxy-ethylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid 226

Example 38

3-(4-{5-(4-*tert*-Butoxycarbonylmethoxy-phenyl)-4-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1-methyl-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 227

Example 39

3-(4-{5-(4-Carboxymethoxy-phenyl)-4-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1-methyl-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid 228

Example 40

3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-(4-ethoxycarbonylmethoxy-phenyl)-1-methyl-1*H*-imidazol-2-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 229

Example 41

3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-(4-ethoxycarbonylmethoxy-phenyl)-1-methyl-1*H*-imidazol-2-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid 230

Example 42

3-(4-{4-(4-Carboxymethoxy-phenyl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1-methyl-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid 231

Example 43

[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-(4-ethoxycarbonylmethoxy-phenyl)-imidazol-1-yl]-acetic acid *tert*-butyl ester 232

Example 44

[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-(4-ethoxycarbonylmethoxy-phenyl)-imidazol-1-yl]-acetic acid 233

Example 45

{4-(4-Carboxymethoxy-phenyl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-imidazol-1-yl}-acetic acid 234

Example 46

3-(4-{4-(4-*tert*-Butoxycarbonylmethoxy-phenyl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 235

Example 47

3-(4-{4-(4-Carboxymethoxy-phenyl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid 236

Example 48

(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-pyridin-3-yl-1*H*-imidazol-4-yl}-phenoxy)-acetic acid *tert*-butyl ester 237

Example 49

(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-pyridin-3-yl-1*H*-imidazol-4-yl}-phenoxy)-acetic acid 238

Example 50

3-(4-{2-(4-Diethylamino-phenyl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid 239

Example 51

3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-(4-pyrrolidin-1-yl-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 240

Example 52

3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-(4-pyrrolidin-1-yl-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid 241

Example 53

(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-[4-((E)-2-*tert*-butoxycarbonyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenoxy)-acetic acid *tert*-butyl ester 242

Example 54

(4-{2-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenoxy)-acetic acid 243

Example 55

3-[4-(4-(4-*tert*-Butoxycarbonylmethoxy-phenyl)-5-{4-[(E)-2-(hexadecyl-methyl-carbamoyl)-vinyl]-phenyl}-1H-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 244

Example 56

3-[4-(4-(4-Carboxymethoxy-phenyl)-5-{4-[(E)-2-(dodecyl-methyl-carbamoyl)-vinyl]-phenyl}-1H-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid 245

Example 57

3-(4-{4-(4-*tert*-butoxycarbonylmethoxy-phenyl)-5-[4-(2-hexadecylcarbamoyl-cyclopropyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 246

Example 58

3-(4-{4-(4-Carboxymethoxy-phenyl)-5-[4-(2-hexadecylcarbamoyl-cyclopropyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid 247

Example 59

(E)-3-{4-[4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-(4-dodecylcarbamoyl-phenyl)-1*H*-imidazol-2-yl]-phenyl}-acrylic acid 111

Example 60

3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-(2,3,4-trimethoxy-phenyl)-1*H*-imidazol-4-yl]-phenyl}-acrylic acid 248

Example 61

(E)-3-(4-{5-[4-((E)-2-Hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-acrylic acid *tert*-butyl ester 249

Example 62

(E)-3-(4-{5-[4-((E)-2-Hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-acrylic acid 250

Example 63

3-(4-{5-[4-(2-Hexadecylcarbamoyl-ethyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-propionic acid 251

Example 64

3-(4-{4-[4-((E)-2-*tert*-Butoxycarbonyl-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 252

Example 65

3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid 253

Example 66

(E)-3-(4-{2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-acrylic acid *tert*-butyl ester 254

Example 67

(E)-3-(4-{2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-acrylic acid 255

Example 68

(E)-3-(4-{2-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-acrylic acid 256

Example 69

3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-dodecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid 257

Example 70

3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-dodecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-isoxazole-5-carboxylic acid 258

Example 71

3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester 259

Example 72

3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-isoxazole-5-carboxylic acid ethyl ester 260

Example 73

3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-isoxazole-5-carboxylic acid 261

Example 74

3-[4-(4-[4-((E)-2-*tert*-Butoxycarbonyl-vinyl)-phenyl]-5-{4-[2-(4-heptyl-phenylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 262

Example 75

3-[4-(4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-{4-[2-(4-heptyl-phenylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid 263

Example 76

3-(4-{4-[4-((E)-2-*tert*-Butoxycarbonyl-vinyl)-phenyl]-5-[4-(2-dihexylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 264

Example 77

3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-dihexylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid 265

Example 78

(E)-3-[4-(5-{4-[(E)-2-(4-Heptyl-phenylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenyl]-acrylic acid *tert*-butyl ester 266

Example 79

(E)-3-[4-(5-{4-[(E)-2-(4-Heptyl-phenylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenyl]-acrylic acid 267

Example 80

(E)-3-(4-{5-[4-((E)-2-Dihexylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-acrylic acid *tert*-butyl ester 268

Example 81

(E)-3-(4-{5-[4-((E)-2-Dihexylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-acrylic acid 269

Example 82

3-[3-(4-{5-[4-((E)-2-Hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-allanoylamino]-propionic acid 160a

Example 83

3-[3-(4-{5-[4-((E)-2-Hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-allanoylamino]-propionic acid 270

Example 84

3-[4-(5-Benzylcarbamoyl-1-hexadecyl-4-phenyl-1*H*-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid 147

Example 85

<u>**3-(4-{4-[4-(*tert*-Butoxycarbonylmethyl-carbamoyl)-phenyl]-5-decyl-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester**</u> **81**

<u>Example 86</u>

<u>**3-(4-{4-[4-(Carboxymethyl-carbamoyl)-phenyl]-5-decyl-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid**</u> **82**

<u>Example 87</u>

Compound **104**

<u>Example 88</u>

Compound **105**

<u>Example 89</u>

<u>**(E)-3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-[4-(2-hydroxy-1-hydroxymethyl-ethylcarbamoyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-acrylic acid *tert*-butyl ester**</u> **94**

<u>Example 90</u>

<u>**(E)-3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-[4-(2-hydroxy-1-hydroxymethyl-ethylcarbamoyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-acrylic acid**</u> **95**

When the compounds of the current invention have asymmetric centers they may occur as racemates, racemic mixtures, and as individual enantiomers or diastereomers, with all isomeric forms being included in the present invention as well as mixtures thereof.

Pharmaceutically acceptable salts of the compounds above, where a basic or acidic group is present in the structure, are also included within the scope of this invention. When an acidic substituent is present, such as –CO_2H, there can be formed the ammonium, sodium, potassium, calcium salt, and the like, for use as the dosage form. Basic groups, such as amino or basic heteroaryl radicals, or pyridyl and acidic salts, such as hydrochloride, hydrobromide, acetate, maleate, palmoate, methanesulfonate, p-toluenesulfonate, and the like, can be used as the dosage form.

Also, in the case of the –CO_2H being present, pharmaceutically acceptable esters can be employed, e.g., methyl, *tert*-butyl, pivaloyloxymethyl, acetoxymethyl, and the like, and those esters known in the art for modifying solubility or hydrolysis characteristics for use as sustained release or prodrug formulations.

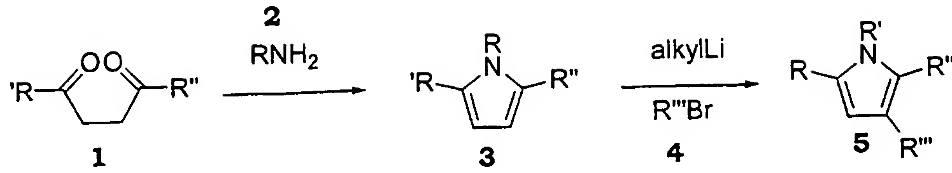
In addition, some of the compounds of the instant invention may form solvates with water or common organic solvents. Such solvates are encompassed within the scope of the invention.

The term "therapeutically effective amount" shall mean that amount of drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

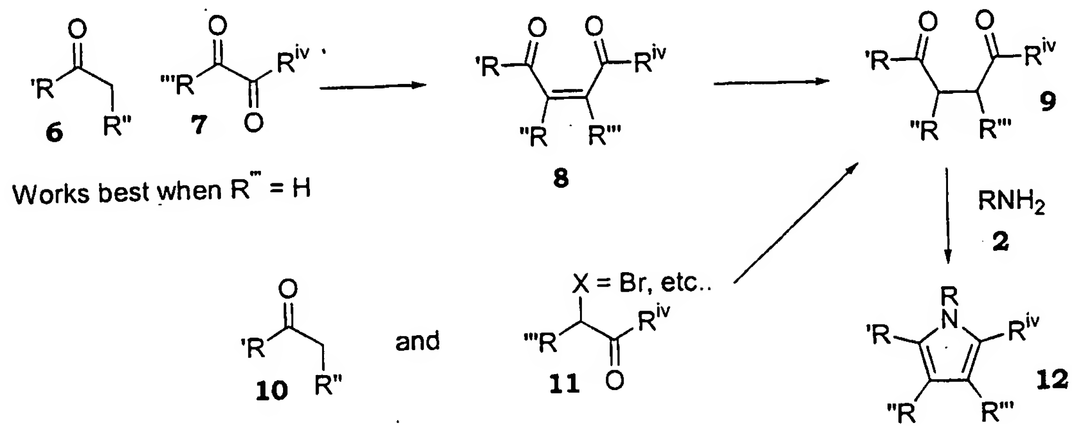
Synthetic Procedures

General references to methodologies for the synthesis of the compounds of the present invention are described in the following references 1) Drayton, C. J., *Comprehensive Heterocyclic Chemistry*, 1st ed; Pergamon: Oxford, 1984 and 2) Joule, J. A.; Mills, K.; and Smith, G.F., *Heterocylic Chemistry*, 3rd ed; Chapman and Hall, 1995.

The synthesis of the pyrrole, thiophene and furan templates is well documented. An example of the synthesis of the pyrrole **3** and **12** template (*via* the Paal Knorr) synthesis, which involves the reaction of 1,4 dicarbonyl compounds **1** and **9** and primary amines **2** is shown below (Schemes 1 and 2) (Wynberg, *Acc. Chem. Res.*, 4, p65 (1971)).



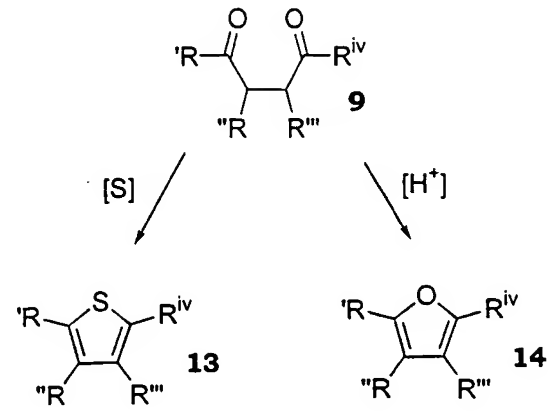
Scheme 1



Scheme 2

Substituted pyrroles can also be made through intermediates generated *via* the Ugi reaction (Mjalli *et al*, *Tetrahedron Lett.*, 37, p2943 (1996)).

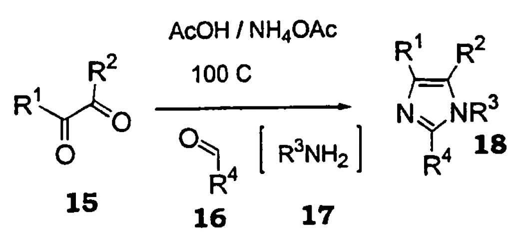
The thiophene and furan templates can also be synthesized using similar chemistry to that shown for the pyrroles (Schemes 1 and 2). The thiophene template can be made *via* the reaction of 1,4-dicarbonyl compounds and a source of sulfur (1,4-dicarbonyl synthesis illustrated in Scheme 3). Lawesson's reagent has been reported as the reagent of choice to effect this transformation (Shridar *et al*, *Synthesis*, 1061 (1982)). The furan template can also be made from the dehydration of 1,4 dicarbonyl compounds (the Paal-Knorr synthesis), usually using non-aqueous acidic conditions (Nowlin *et al*, *J. Am. Chem. Soc.*, 72, p5754 (1950); Traylelis *et al*, *J. Org. Chem.*, 29, p123, (1964); Scott *et al*, *Synthesis*, p209 (1973)) (Scheme 3).



Scheme 3

More specific examples of, and references to, methodologies for the preparation of the oxazole and imidazole can be found in Gauthier *et al*, *Bioorg. & Med. Chem.*, 6, 87-92, (1996); Maduskuie *et al*, *J. Med. Chem.*, 38, 1067-1083 (1995); Mjalli *et al*, *U.S. Patent*, 5 753 687 (Application Number 766 114).

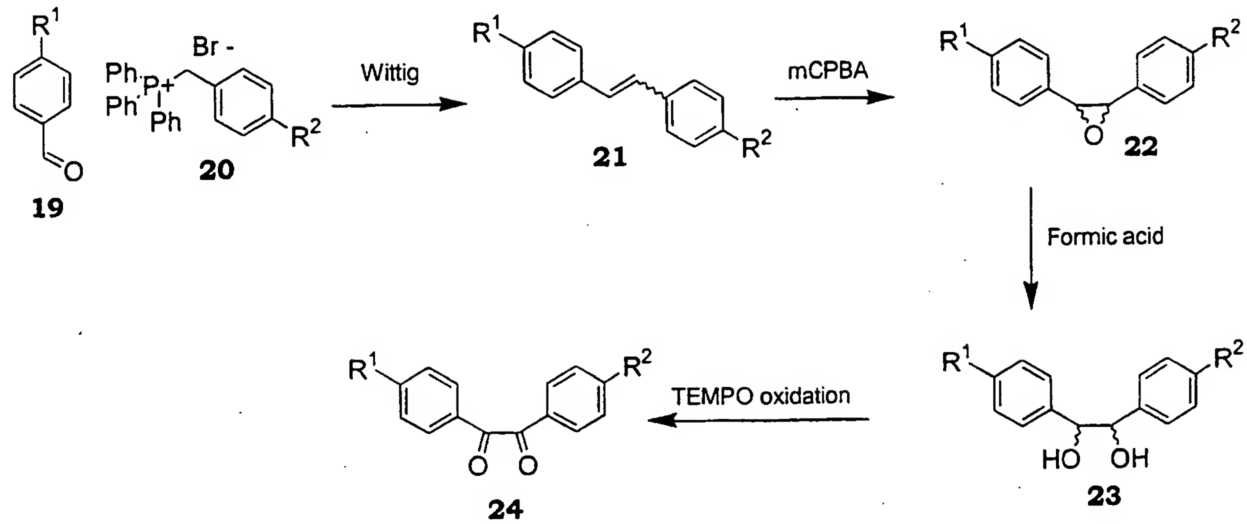
The reaction sequence shown in Scheme 4 can be utilized to synthesize tri- or tetra-substituted imidazole derivatives **18**. The reaction of a dione **15** with an aldehyde **16**, with the addition of an alkyl amine **17** for N-substituted imidazoles (this reaction is not regioselective and will give a mixture of two compounds) in the presence of ammonium acetate and acetic acid gives the imidazole **18** in good yield.



Scheme 4

A number of methods can be used to synthesize the dione intermediates. Scheme 5 illustrates a general methodology for the synthesis

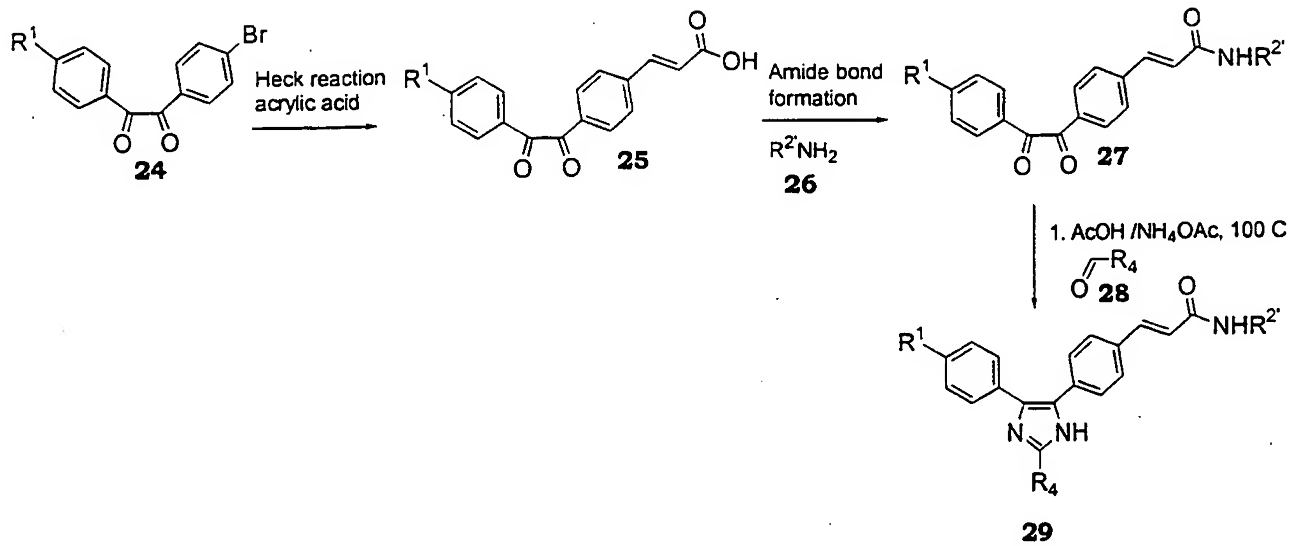
of dione **24**, from readily available starting materials, utilizing a Wittig reaction.



Scheme 5

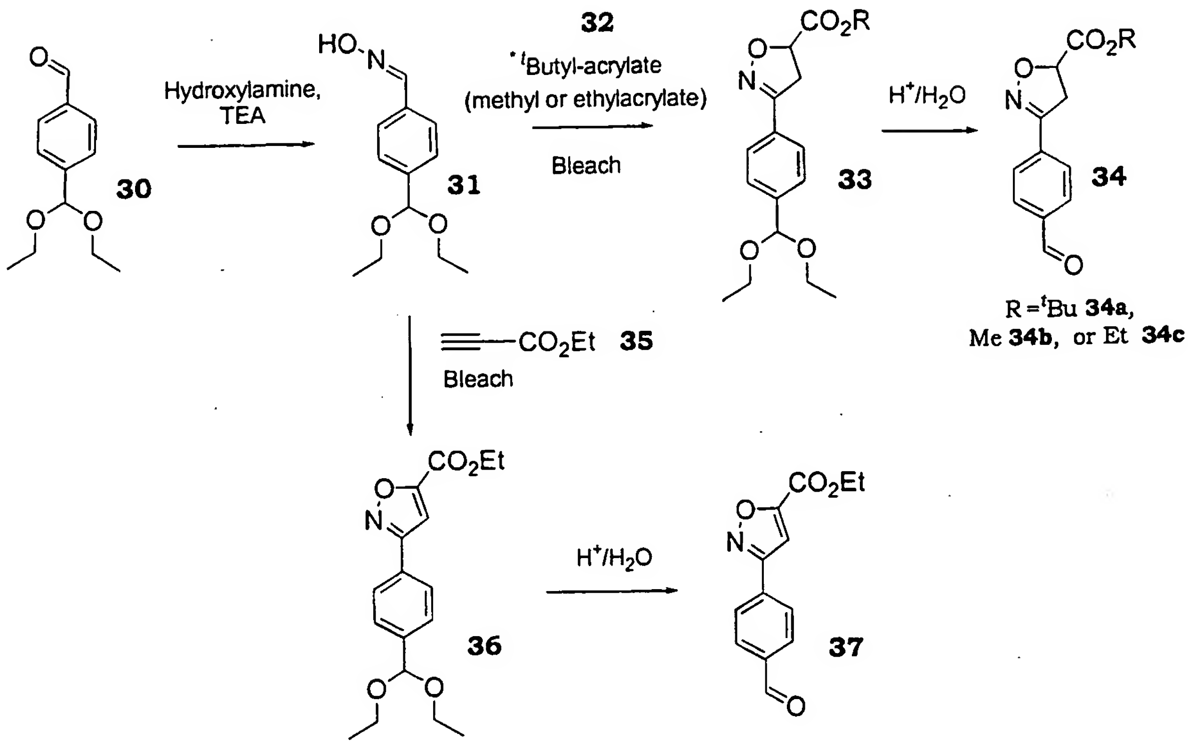
Aldehyde **19** is reacted with the Wittig reagent **20** to give the alkene **21**. The double bond of **21** is then oxidized to the epoxide **22**, which in turn is hydrolyzed to the diol **23** *via* treatment with formic acid and subsequent hydrolyses of the resulting formic acid ester intermediate during workup. The diol **23** is then oxidized to the required dione **24** *via* a TEMPO oxidation. This dione **24** can be used directly to form an imidazole as illustrated below in Scheme 6.

General derivatization of intermediate diones such as **24** can be achieved *via* a Heck reaction for example. The Heck reaction can be used to attach an acrylamide side chain as a desired R group to give compounds such as cinnamic acid **25**, or a cinnamic acid ester. The resulting acid or esters can themselves be derivatized, an example being *via* condensation with an amine (after hydrolyses of the ester if esterified) to form an amide **27**, as illustrated in Scheme 6.



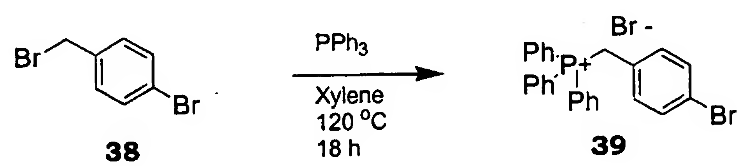
Scheme 6

An example of the synthesis of a non-commercially available aldehyde as a starting material for Scheme 5 is illustrated in Scheme 7. Terephthalaldehyde mono-diethyl acetal **30** is treated with hydroxylamine and triethylamine (TEA) to give the corresponding oxime **31**. This oxime **31** after oxidation with bleach undergoes a 3 + 2 cycloaddition reaction with *t*-butyl (methyl or ethyl) acrylate **32** to afford the 4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester **33**. The diethyl acetal- protecting group of **33** is then removed *via* acid hydrolyses to reveal the aldehyde **34**. The isoxazole **37** can be synthesized in a similar manner using the alkyne **35** in place of the alkene **32**.



Scheme 7

A general procedure for the synthesis of the Wittig reagent **39** as starting material for Scheme 5 is outlined in Scheme 8.

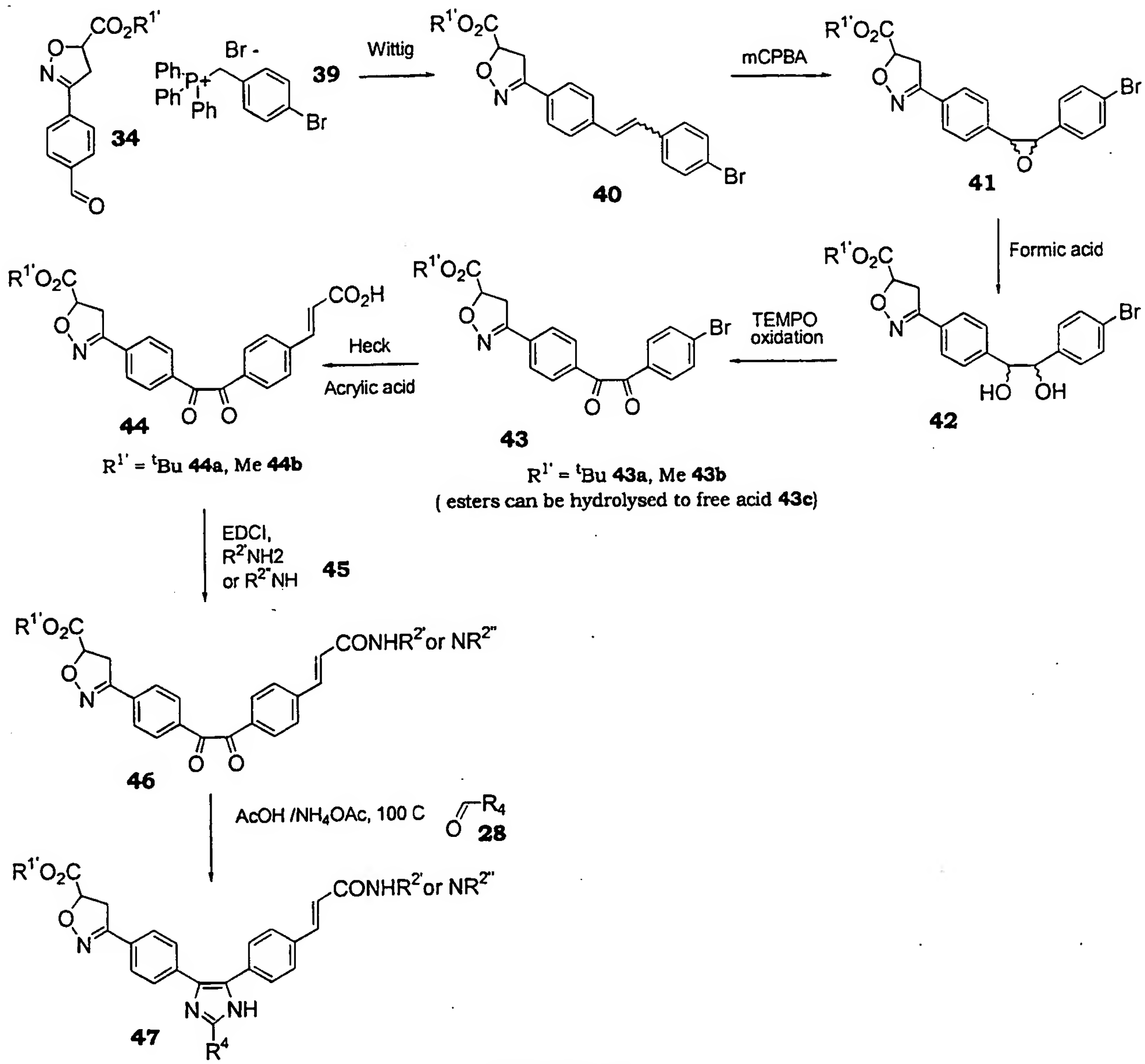


Scheme 8

Schemes 9, 10 and 11 illustrate specific examples of the synthesis of imidazoles, as described in the current invention, using the general methods outlined in Schemes 5 and 6.

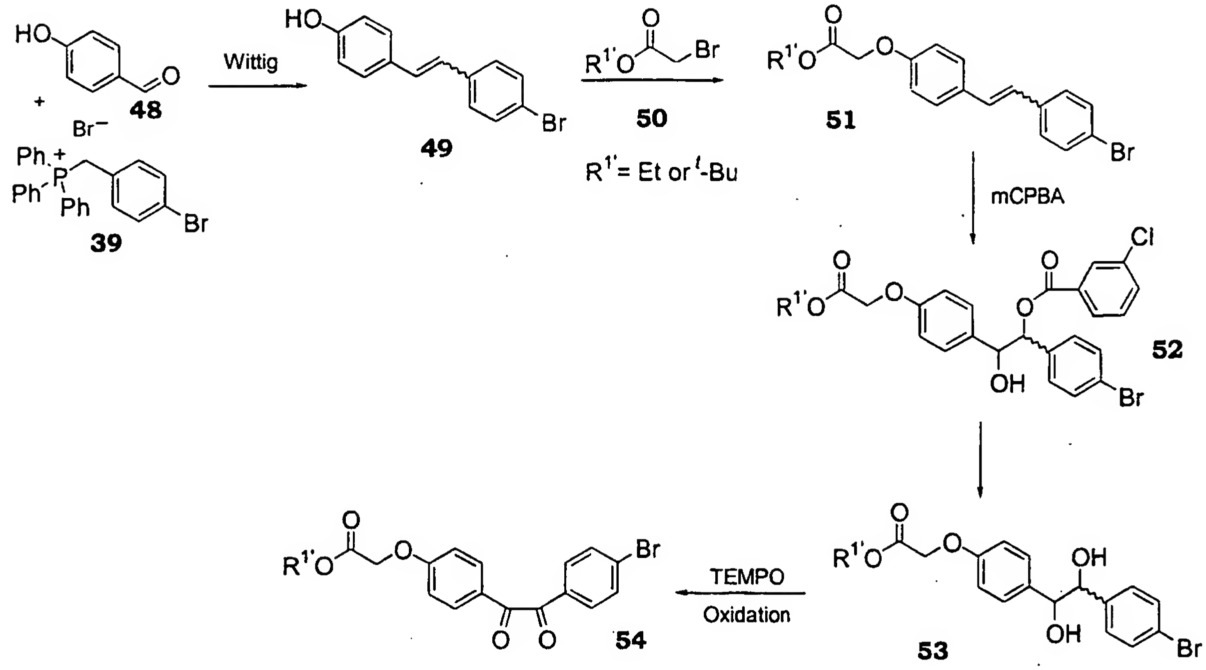
In Scheme 9 aldehyde **34** is reacted with Wittig reagent **39**, to give alkene **40**. This alkene is oxidized with mCPBA to the epoxide **41**. The epoxide **41** is opened to give the diol **42**, which is in turn oxidized to the dione **43**. The dione **43** can be functionalized *via* a Heck reaction with acrylic acid, to give the cinnamic acid derivative **44**. This acid **44** can the be

condensed with an amine **45** to give the derivatized dione **46**, which can then be used to make the imidazole **47**.



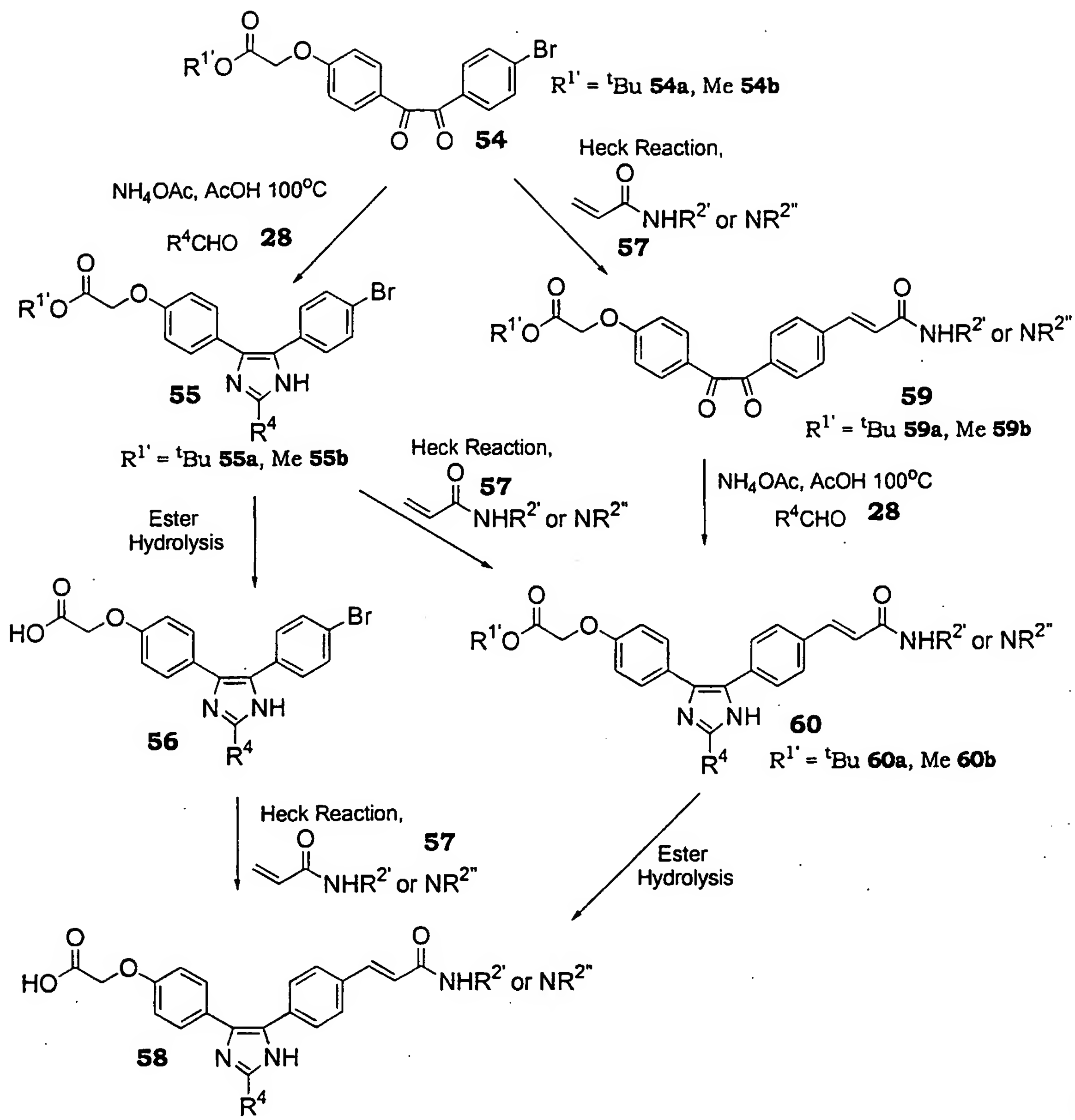
Scheme 9

Scheme 10 illustrates a dione synthesis which includes a step for the derivatization of the intermediate alkene **49** to give ultimately a phenoxy acetic acid dione **54** which has been used routinely for the synthesis of imidazole compounds described in the current invention.



Scheme 10

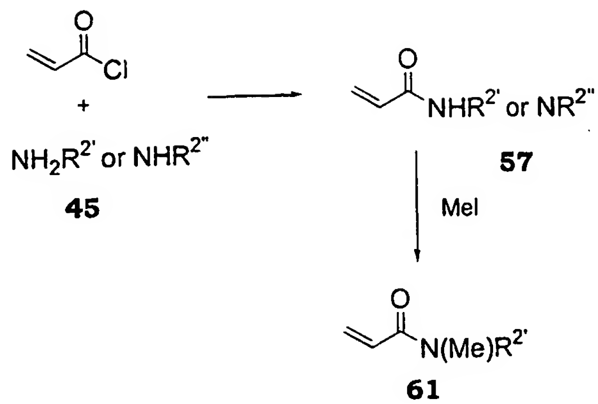
Scheme 11 illustrates the use of dione **54** for imidazole synthesis. The dione can be derivatized to the acrylamide **59** and then converted to imidazole **60**. The imidazoles **55** and **56** can be derivatized by direct attachment of an acrylamide **57** (that is made *in situ* from the appropriate amine and acroyl chloride) to give imidazoles **60** and **58** respectively. Imidazole **60** can be converted to imidazole **58** by ester hydrolysis.



Sc

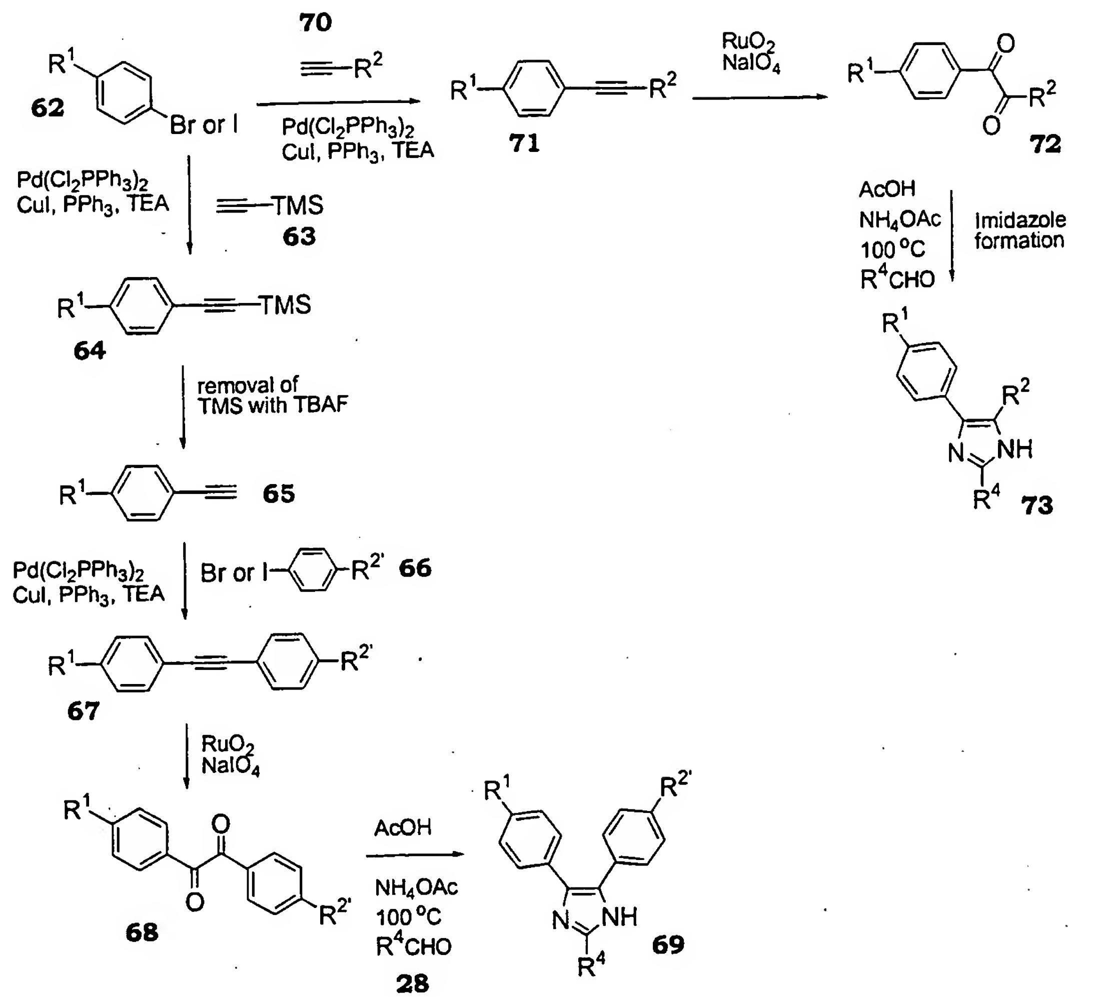
heme 11

Scheme 12 illustrates the synthesis of the acrylamide **57**. Acroyl chloride is reacted with the appropriate amine **45** to give the acrylamide **57** quantitatively in most cases. This acrylamide **57** can be derivatized by alkylation of the amide NH with iodomethane to give the acrylamide **61** if required. These acrylamides **57** and **61** can then be used directly in the Heck reactions without purification.



Scheme 12

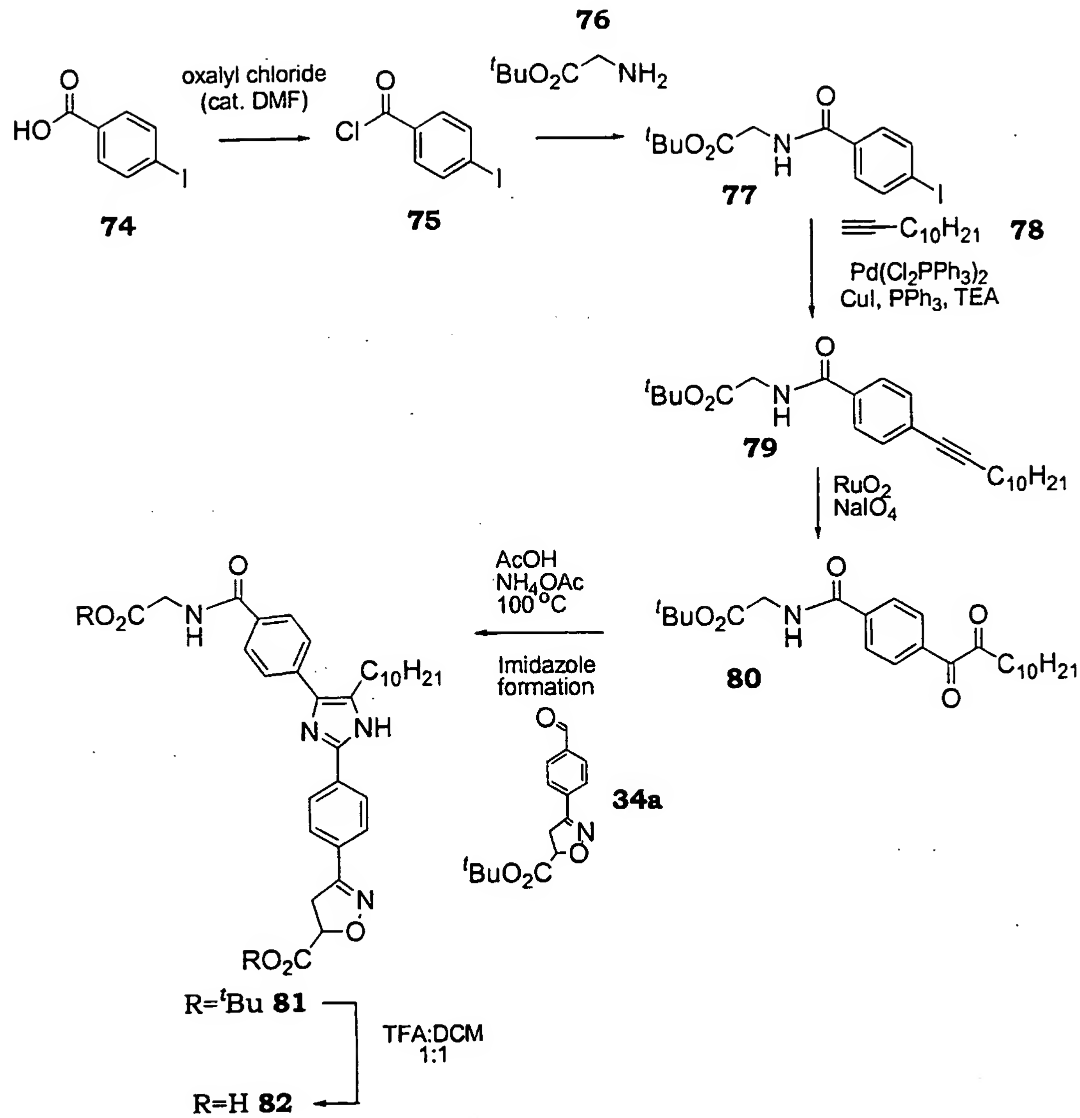
Unsymmetrical diones can also be synthesized through a process which starts with a Sonogashira palladium coupling reaction between an aryl halide **62** and an alkyne **70** or TMS-alkyne **63** to give compounds **71** and **64** respectively. Alkyne **71** can be oxidized directly to the dione **72** using ruthenium tetroxide, then utilized for imidazole synthesis to give imidazole **73**. If TMS-alkyne **63** is used, removal of the 'TMS' group with TBAF to give alkyne **65** can be followed with a second Sonogashira coupling to aryl halide **66** followed by oxidation with ruthenium tetroxide to give an unsymmetrical diaryl dione **68** which can then be used for the synthesis of imidazole **69** as illustrated in Scheme 13.



Scheme 13

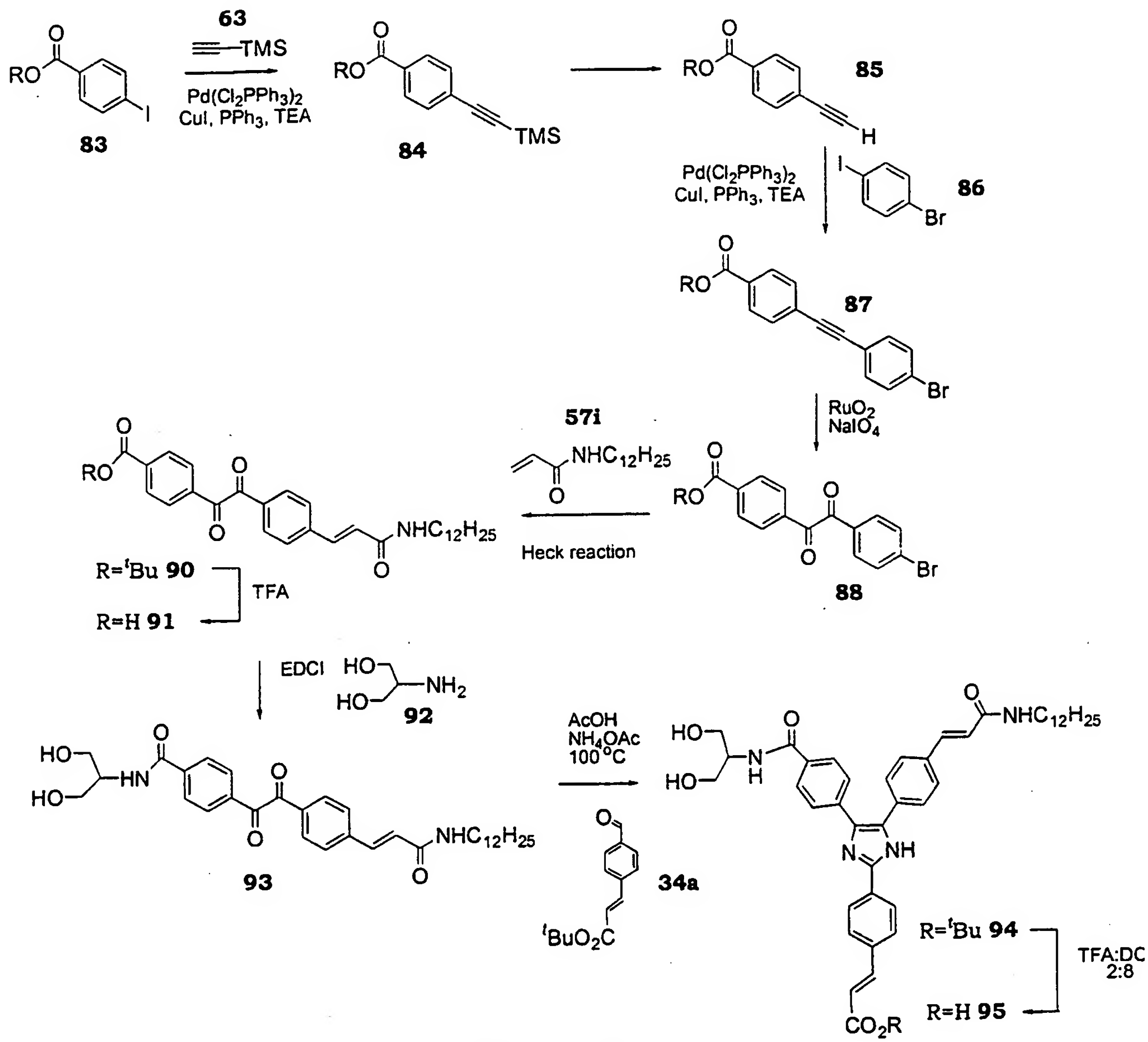
Specific examples of the synthesis of imidazole derivatives synthesized *via* the methodologies outlined in Scheme 13 are shown in Schemes 14, 15 and 16.

Scheme 14 shows the conversion of 4-iodobenzoic acid **74** to the acylchloride **75**. This acylchloride **75** is reacted without purification with the *tert*-butyl ester of glycine **76**, to give the amide **77**. Compound **77** is then coupled to 1-dodecyne **78** to give the alkyne **79**. This alkyne **79** is then oxidized to the dione **80** with ruthenium tetroxide. Dione **80** can then be used for the synthesis of imidazole **81** which after treatment with TFA gives the imidazole **82**.



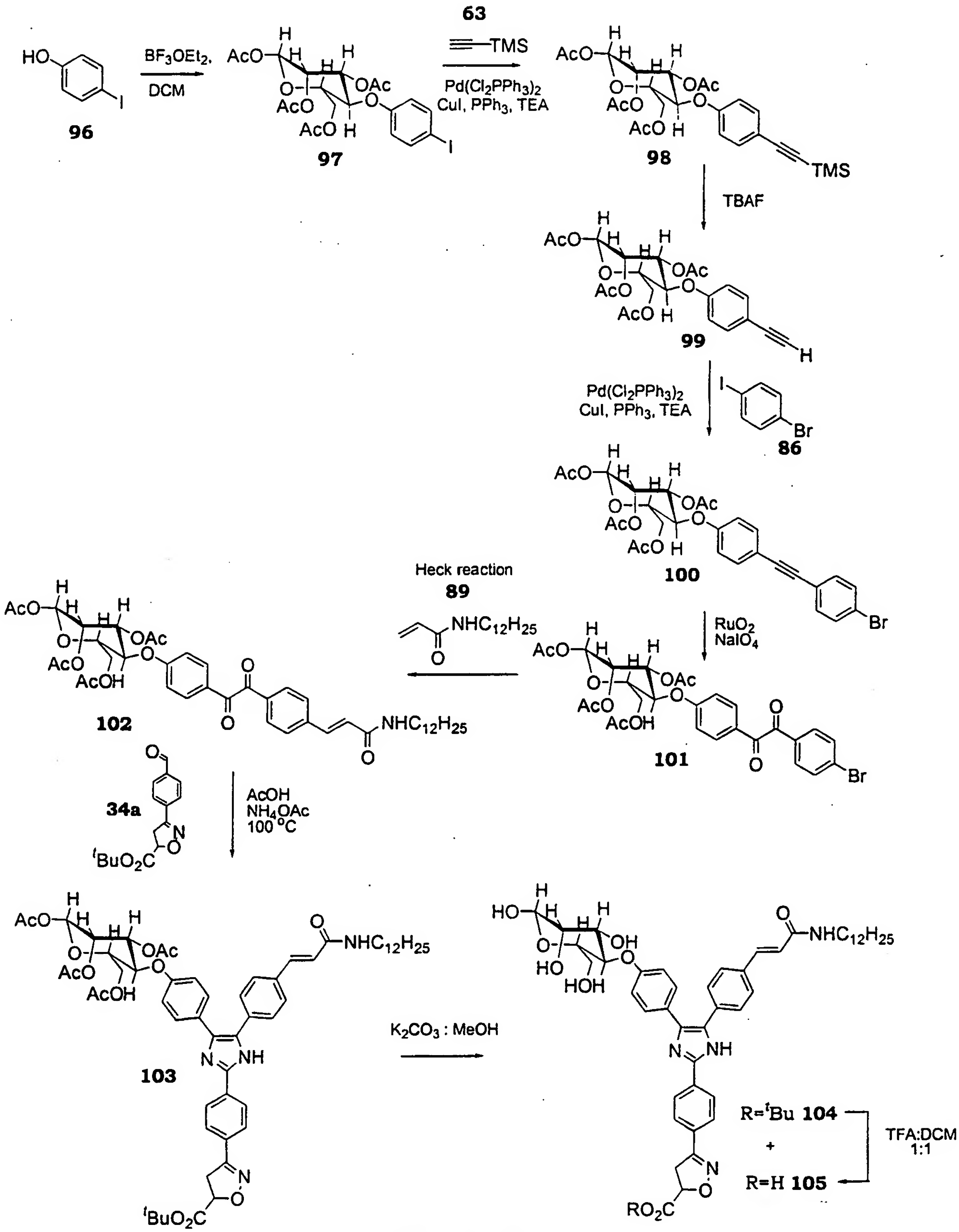
Scheme 14

Scheme 15 shows the synthesis of the imidazoles **94** and **95** which contain a diol moiety.



Scheme 15

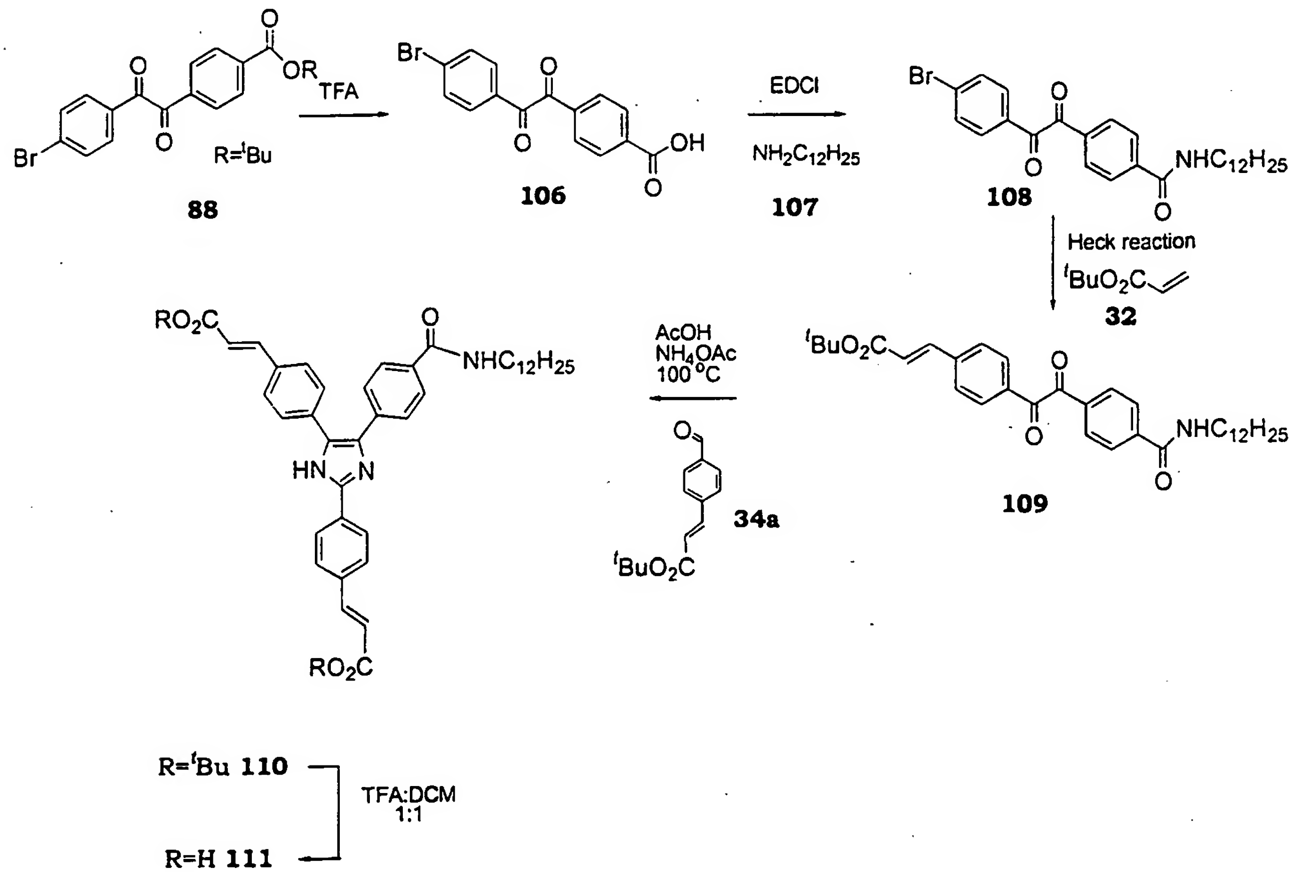
Scheme 16 shows the synthesis of the imidazoles **104** and **105** which contain a mannose moiety. The intermediate dione **88** is also used in Scheme 17.



Scheme 16

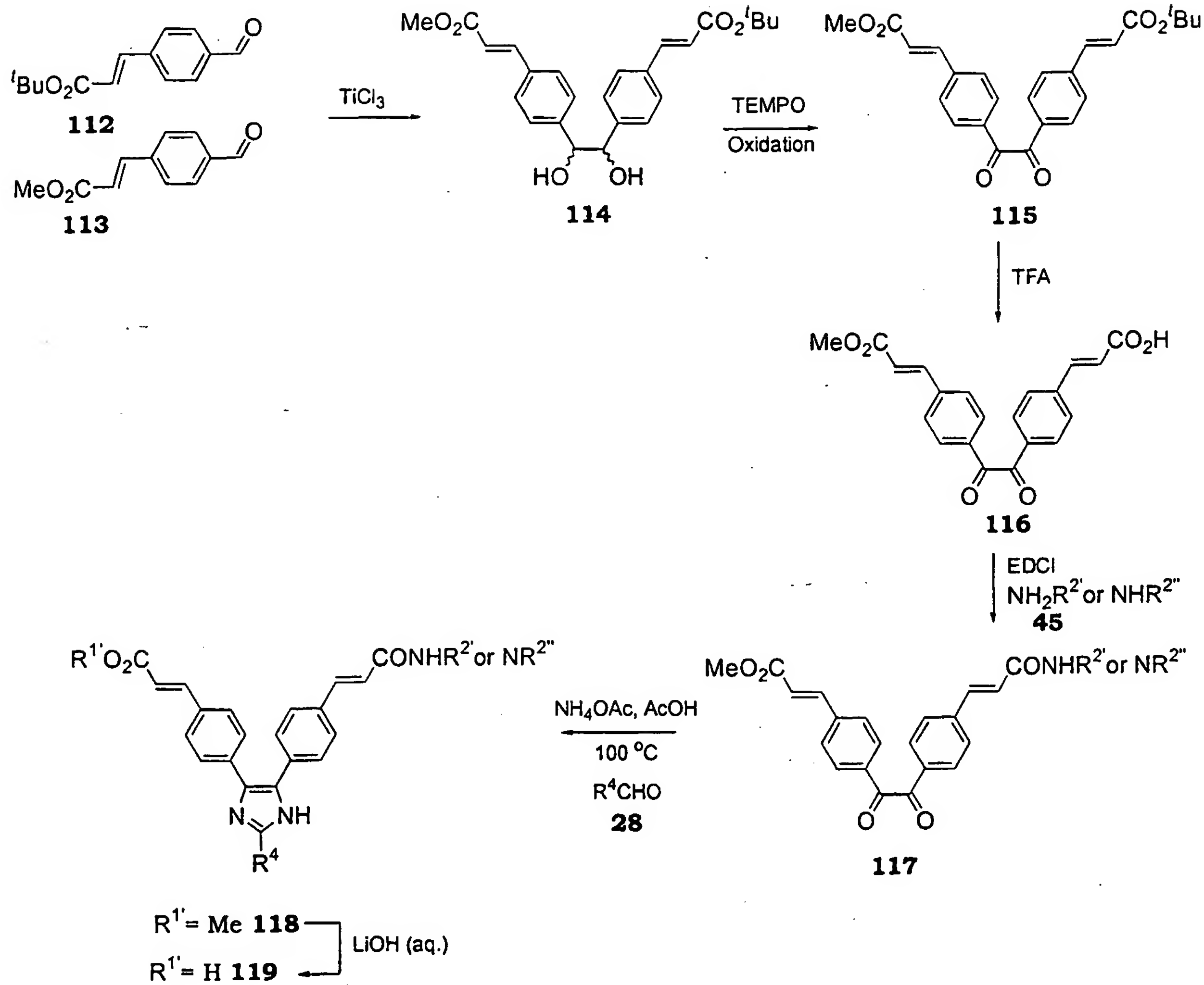
The intermediate dione **88** is used in a different way in Scheme 17 than in Scheme 16, with derivatization of the carboxylic acid moiety to a hydrophobic side chain, instead of a polar or hydrophilic side chain, to give

dione **108**. This dione **108** can be further derivatized *via* a Heck reaction to dione **109**. Dione **109** can then be used to synthesize imidazoles **110** and **111**.



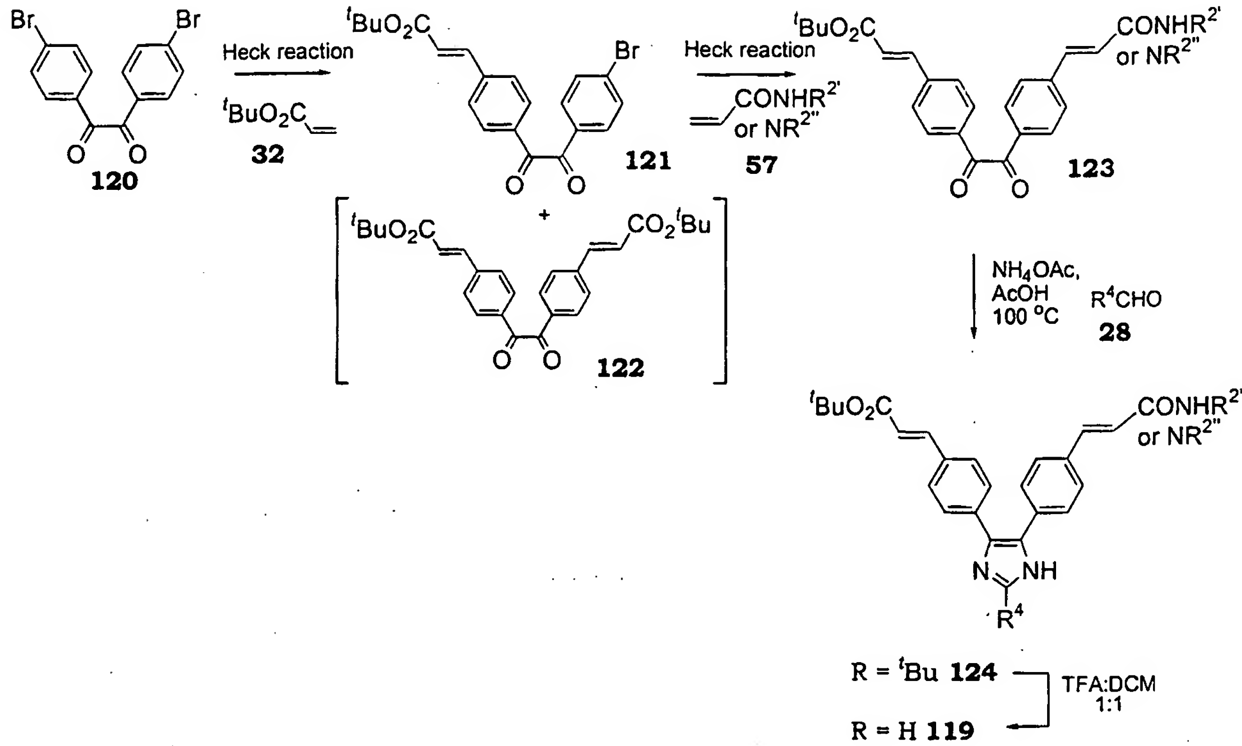
Scheme 17

Other diones of interest are represented by the bis-cinnamate **115**. This type of dione can be synthesized in a number of ways. Schemes 18 and 19 represent two appraoches. Scheme 18 shows how dione **115** can be synthesized *via* the condensation of the two aldehydes **112** and **113**. The unsymmetrical diol **114** can be isolated and oxidized to the dione **115**. This dione **115** can be converted in two steps to dione **117**. This dione can then be used to synthesize imidazoles **118** and **119**.



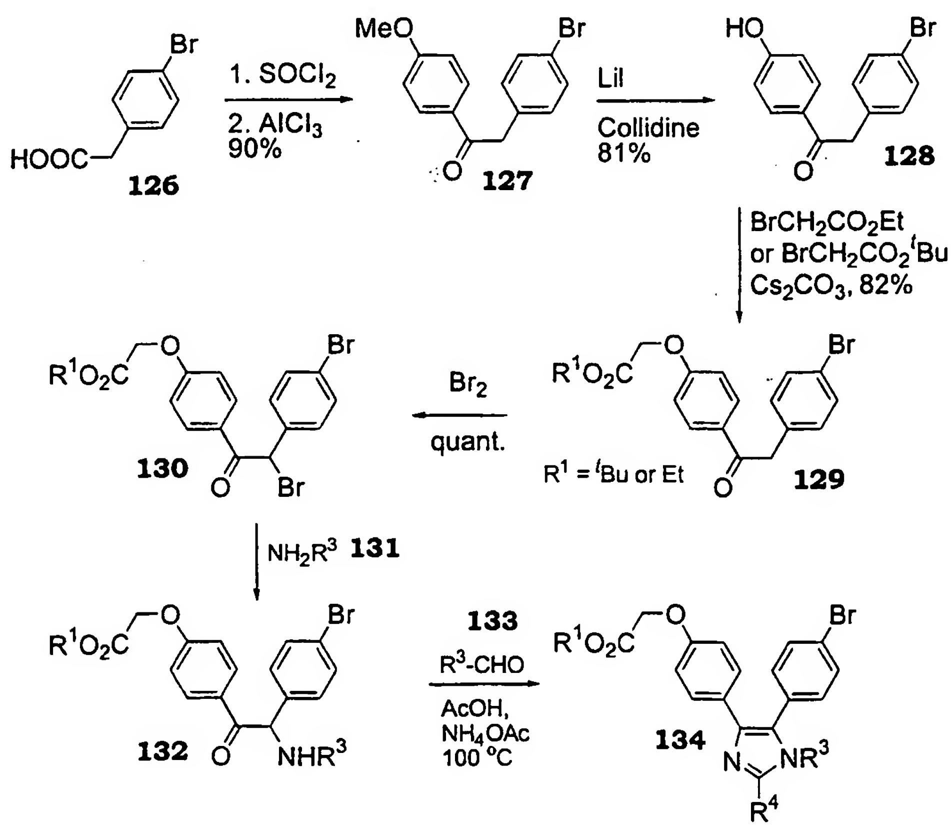
Scheme 18

Scheme 19 shows how bis-cinnamates can be synthesized *via* sequential Heck reactions to give dione **123** which can then be used to synthesized imidazoles **124** and **119**.



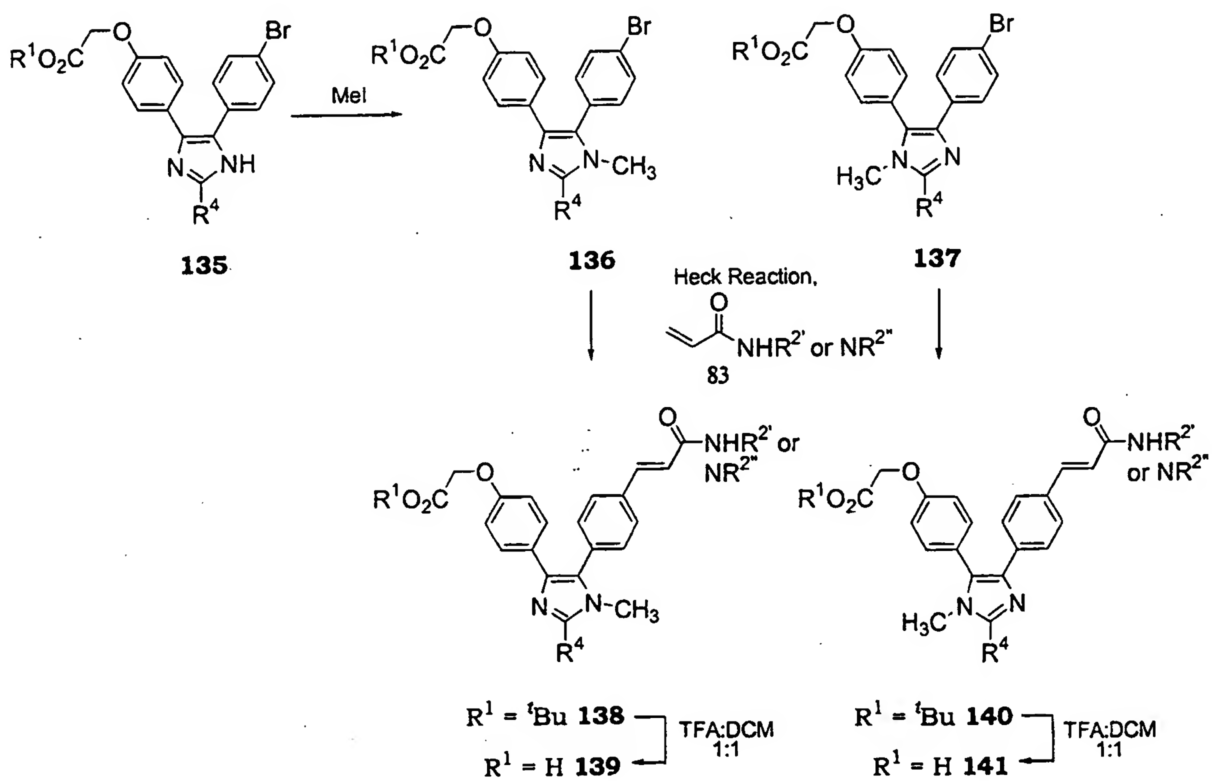
Scheme 19

Tetrasubstituted imidazoles **134** can be synthesized regiospecifically *via* the keto-bromide intermediate **130** as illustrated in Scheme 20. The *N*-substituted imidazoles are also readily accessible *via* direct alkylation or acylation of the imidazole nitrogen as illustrated in Scheme 21.



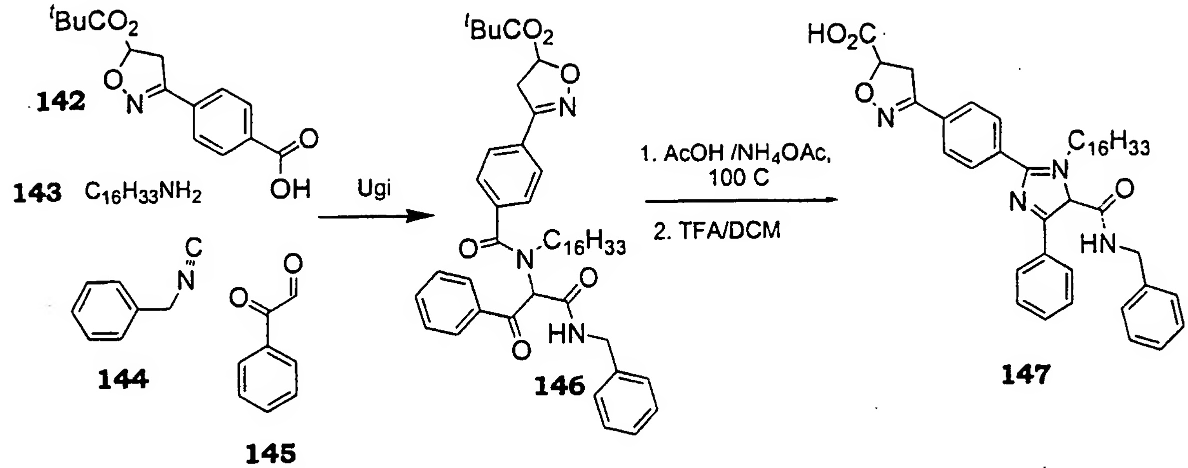
Scheme 20

Scheme 21 shows the direct alkylation of the imidazole **135** nitrogen with iodomethane, to give a separable mixture of N-alkylated imidazoles **136** and **137**. A Heck reaction installs an acrylamide to give imidazoles **138** and **140** which after removal of the *tert*-butyl esters gives imidazoles **139** and **141** respectively.



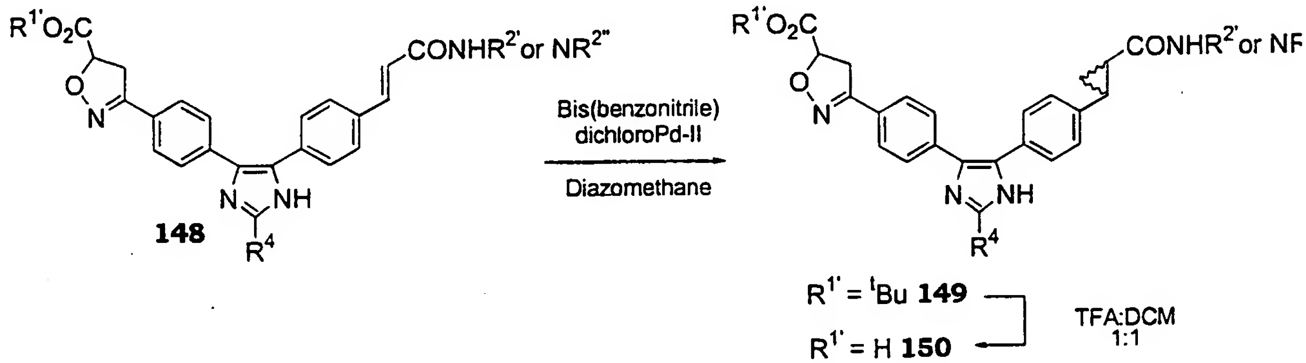
Scheme 21

The Ugi reaction can also be employed to synthesize Ugi intermediates that can be cyclized to give tetra-substituted imidazoles (Zhang *et al*, *Tetrahedron Lett.*, 37, p751 (1996)). A specific example of the use of this approach is shown below in Scheme 22.



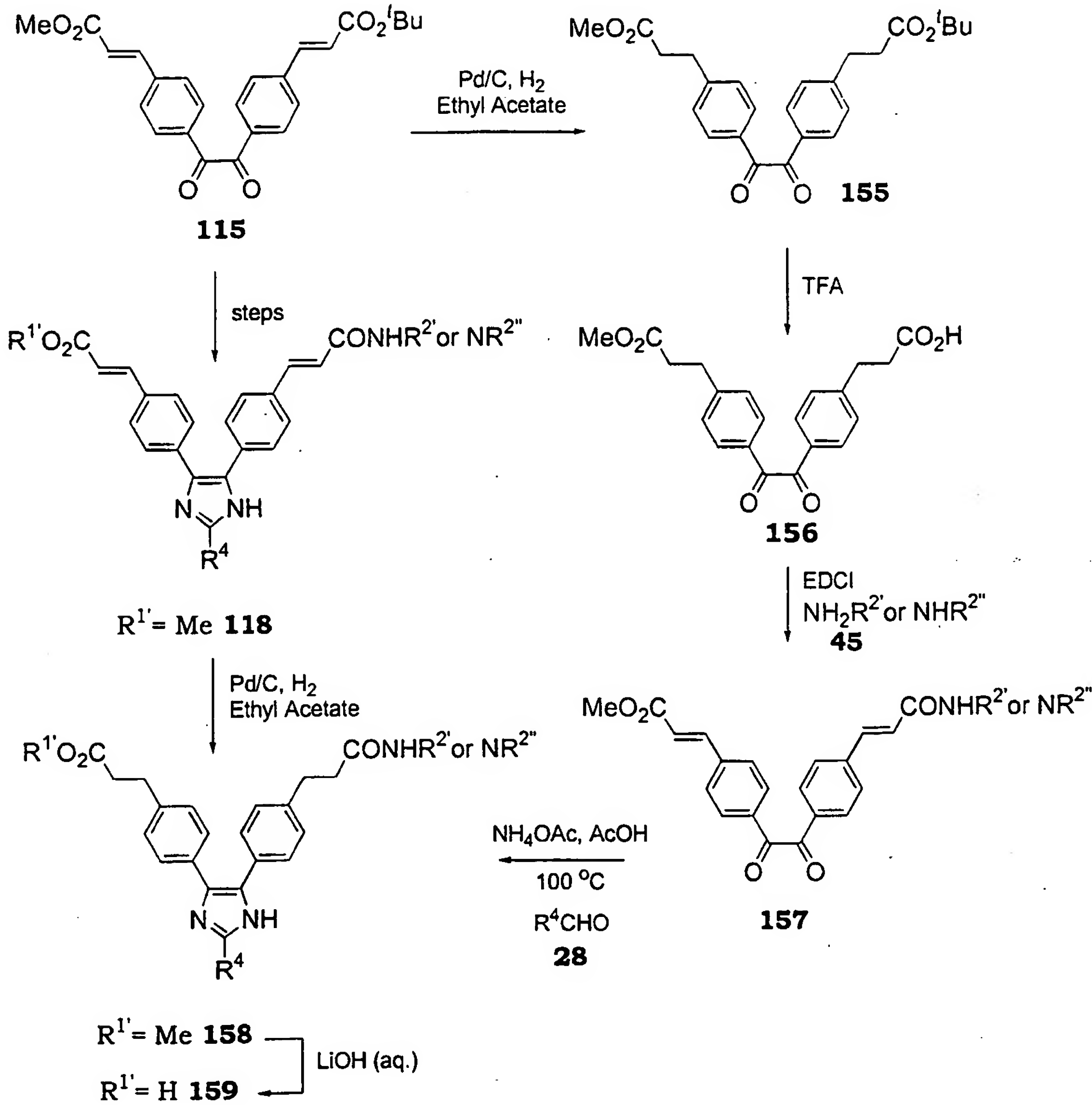
Scheme 22

Imidazoles can be further derivatized. The double bond of imidazole **148** can be converted to the cyclopropyl *via* treatment with Pd II and diazomethane as shown in Scheme 23.

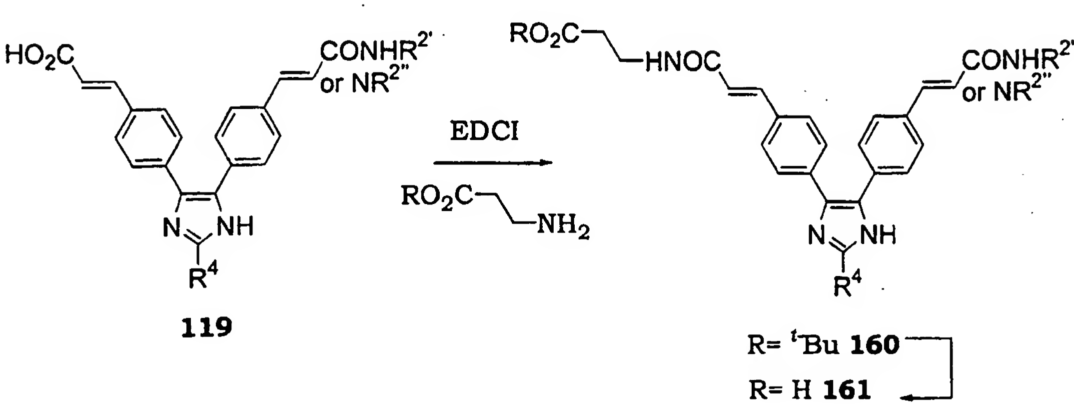


Scheme 23

Double bonds can also be reduced on the imidazole **118** or the dione **115** for example, to give the saturated alkyl chain, using Pd/C and hydrogen gas in ethyl acetate as illustrated in Scheme 24.



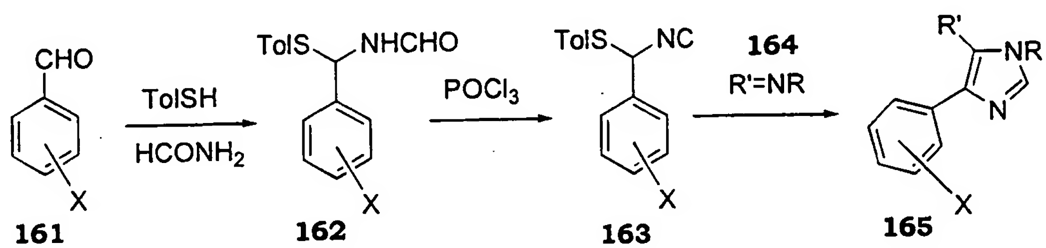
Scheme 24



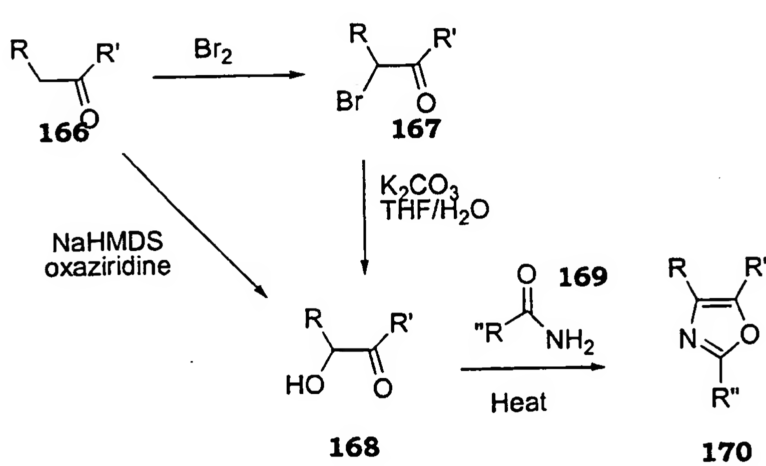
Scheme 25

The final imidazole can be further derivativatized to compounds of the current invention by reaction of the acid moiety with an amine for eample as shown in Scheme 25.

Alternative methodologies for the synthesis of the imidazole template include the reaction sequence shown in Scheme 26, which illustrates a modified version of van Leusen's methodology for imidazole synthesis which proceeds *via* a 1,3-dipolar cycloaddition of the anion of tolyl sulfide isocyanides to imines. This approach leads to tri-substituted N-alkylated imidazoles (Gallagher *et al, Bioorganic and Med.Chem.* 5; 49-64 (1997)). Tosylmethyl isocyanide has been used in the synthesis of all three 1,3-azole types (oxazoles, thiazoles and imidazoles)(van Leusen *et al*; *Tetrahedron Lett.*, p2369 (1972); van Leusen *et al, ibid* p2373; van Leusen *et al, Synthesis*, p501 (1977); van Leusen *et al, J. Org. Chem.*, 42, p1153 (1977)).

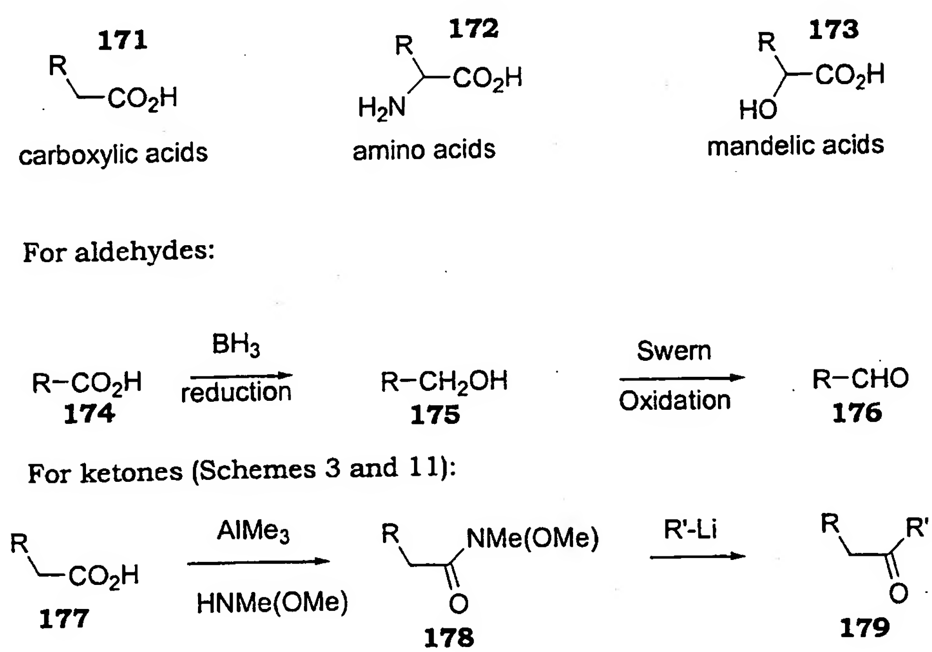


Scheme 26



Scheme 27

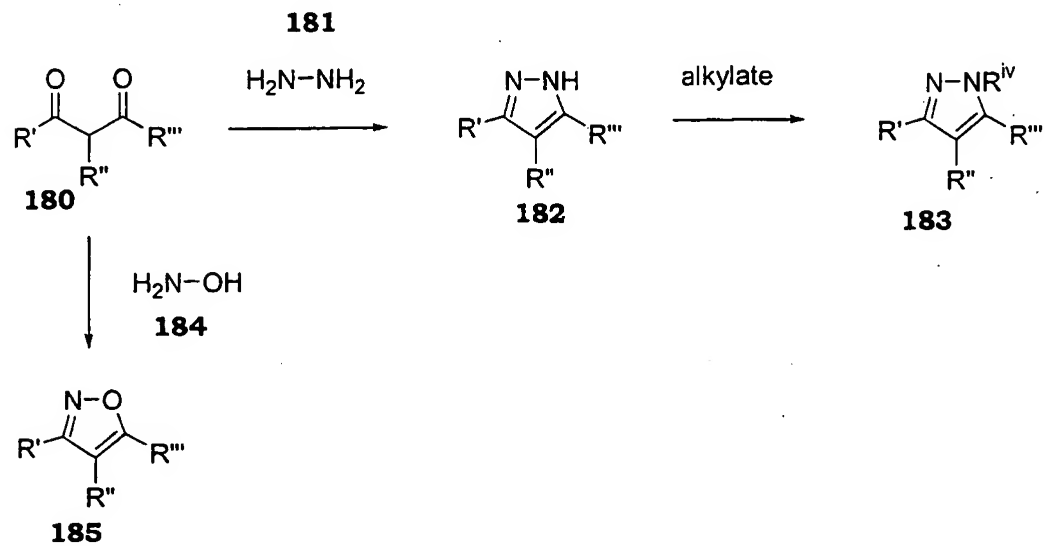
The oxazole template can be synthesized through a common α-halocarbonyl intermediate as illustrated in Scheme 27 (Gauthier *et al*, *Bioorg. & Med. Chem.*, 6, 87-92, (1996); Harris et al *J. Org. Chem*, 27, 2705 (1962); *Helv. Chim. Acta*, 33, 1271, (1950); B. Hulin *et al. J. Med. Chem.* 39, 3897-3907, (1996)). The oxazole template can also be made from amino acid derivatives (Wipf *et al*, *Bioorg. Med. Chem. Lett.*, 5, 165-177 (1997)). The required starting materials for the forgoing synthetic schemes are either commercially available or accessible from readily available starting materials. For example aldehydes and ketones and can be synthesized as shown below (Scheme 28):



Scheme 28

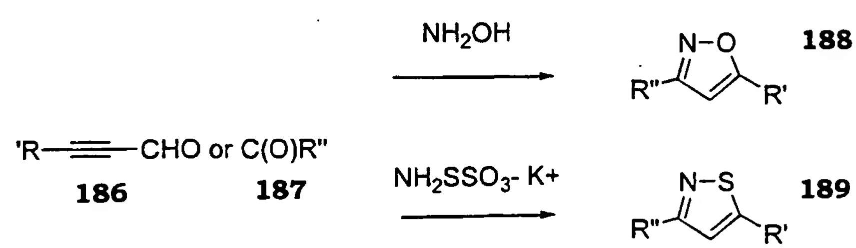
General methodologies to synthesize the pyrazole, isothiazole, and isoxazole templates (1, 2-azoles), include those illustrated below in schemes

29 and 30. Scheme 29 shows a general methodology for the synthesis of the pyrazole template (S. Bourrain *et al*, Bioorg. Med. Chem., 6, 1731-1743 (1998)) and the isoxazole template (Wiley *et al*, *Org. Synth., Coll. Vol. IV*, p351, (1963); Brederick, Chem. Ber., 97, p3407 (1964)).



Scheme 29

The isoxazole and isothiazole templates can also be synthesized *via* an alkyne intermediate (Scheme 30) (Reviews: Quilico *et al*, ed. Wiley, Wiley Interscience, p.1 (1962); Kochetkov *et al*, *Adv. Heterocycl. Chem.*, 14, p 43, (1972); Sokolov, Adv. Heterocycl. Chem., 2, p 365, (1963); Wakefield *et al*, *Adv. Heterocycl. Chem.*, 25, p 147, (1979); Wooldridge, *Adv. Heterocycl. Chem.*, 14, p 1, (1972)).



Scheme 30

Experimental Synthetic Description

To further illustrate the practice of this invention, the following examples are included along with the general methods employed to synthesize the compounds described.

General Experimental Information

Nuclear magnetic resonance spectra (^1H-NMR) were measured on either a Varian (300 MHz) or a Varian (400 MHz). Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS). Data are reported as follows: chemical shift, multiplicity (br=broad, s=singlet, d=doublet, t=triplet, q=quadruplet, m=multiplet), coupling constant (Hz), integration and peak assignment.

Mass spectra were measured using Atmospheric Pressure Chemical Formation (APcI) looking at positive and negative modes on a Micromass LCZ (3 KeV with a probe temperature of 400 °C and a source block at 120 °C).

LC spectra for LC/MS were measured using an eluant of CH_3CN (0.1% CF_3CO_2H)/H_2O (0.1% CF_3CO_2H) (V:V) on a Hewlett Packard HP1100 HPLC, in the range 200-300 nm with a Diode Array Detector (DAD); 5 µl per injection (Gilson 215 Autosampler) at an average concentration of 1 mg/ml; gradient: 10-100% CH_3CN in 5 minutes, 100% CH_3CN for 1 minute, 100-10% CH_3CN in 0.2 minutes, 10% CH_3CN for 1.4 minutes; LC element split 1:4 directly into ion source (500 µl/min).

The chromatography columns used for LC in LC/MS and HPLC were 50 x 4.6 mm C-8 with 5 μm particle sizes and Zorbax 150 x 4.6 mm C-8 with 5 μm particle sizes, respectively. The same gradient was used in HPLC as in LC for LC/MS.

Reactions in solution phase were monitored by thin layer chromatography (TLC) using Merck silica gel 60F-254-coated plates (0.25 mm thickness). Flash chromatography was performed using E. Merck silica gel 60 (230-400 mesh ASTM).

Synthetic Methods

General Methods

General Method 1: **Synthesis of Aldehyde 34** (Scheme 7)

General procedure for synthesis of oxime 31:

The aldehyde **30** (10 g, 48 mmol) was dissolved in dioxane (40 mL). Triethylamine (20 mL) was added, followed by hydroxylamine hydrochloride (4 g, 58 mmol). The reaction mixture was sonicated for 3 hours then stirred at room temperature about 3 days. The progress of the reaction was monitored by ^{1}H NMR. The reaction was worked up by concentration *in vacuo* to about 50% of the original volume. Water (60 mL) was added and the reaction extracted with diethyl ether (3 x 40 mL). The combined organic extracts were then dried ($MgSO_4$), and concentrated *in vacuo.* The oxime **30** was obtained and used crude in the next reaction (10 g, crude yield, 95%: quantitative by NMR).

Data for compound **30**: ^{1}H NMR (400 MHz, $CDCl_3$); 8.0 (s, 1H), 7.4 (d, 2H, J = 8), 7.3 (d, 2H, J = 8), 5.4 (s, 1H), 3.5 (m, 4H), 1.1 (m, 6H).

General procedure for synthesis of aldehyde **34**:

The oxime **30** (24.9 g, 112 mmol) was dissolved in THF (200 mL). *t*-Butyl acrylate **32** (28.6 g, 223 mmol) was added and the reaction mixture cooled to 0 °C. Bleach (5.25% sodium hypochlorite aq.) (400 mL) was added and the reaction mixture allowed to warm to room temperature. When all of the starting material had been consumed, the reaction was worked up *via* addition of ethyl acetate (200 mL), followed by washing with 10% $Na_2S_2O_3$ (50 mL) and brine (50 mL), dried (Na_2SO_4) and concentration *in vacuo*. The t-butyl acrylate was removed by co-evaporation with toluene (monitored by NMR) to give compound **33**. The acetal protecting group of **33** was removed by dissolving the isoxazoline aldehyde **34** in THF/water (300 mL/50 mL) followed by addition of acidic amberlite IR-120 ion-exchange resin (2 g). The reaction mixture was stirred at room temperature for 5 hours. The resin was then removed *via* filtration and the product extracted with DCM. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The aldehyde **34** was obtained as a pale yellow crystalline solid, which was recrystallized from DCM/Hexane (22 g, 92% yield).

Data for compound **34**: ^1H NMR (400 MHz, $CDCl_3$); mixture of isomers: 10.01 (s, 1H), 7.95 (d, 2H, J = 8.1), 7.85 (d, 2H, J = 8.1), 5.1 (t, 1H, J = 9.6), 3.61 (d, 2H, J = 9.6), 1.5 (s, 9H).

General Method 2: **Synthesis of Wittig reagent 39** (Scheme 8)

4-Bromobenzyl bromide **38**(10 g, 40 mmol) was added to triphenyl phosphine (11 g, 42 mmol), in *o*-xylene (50 mL). The mixture was heated to

150 °C overnight. The Wittig reagent **39** crystallizes out of solution and is collected by filtration as a white crystalline solid, which is washed with hexane and dried in a dessicator before use. The yield is quantitative.

General Method 3: **Synthesis of dione 43 *via* Wittig reacton** (Scheme 9)

Wittig reaction to give alkene **40**:

To the Wittig reagent **39** (22.3 g, 43 mmol) in dry DMSO (65 mL), was added potassium *tert*-butoxide (5.14 g, 43 mmol) and the mixture was stirred at R.T. After 30 minutes, the aldehyde **34** (11.4 g, 41 mmol) was added in dry THF (150 mL). The reaction was stirred for 1 hour at R.T., then quenched by pouring into ice water (100 mL). This mixture was then extracted with DCM (3 x 100 mL). The combined DCM extracts were washed with water (50 mL), saturated sodium bicarbonate (50 mL) and brine (50 mL). The mixture was dried over anhydrous sodium sulfate, and concentrated to dryness. The crude product was purified by silica gel chromatography (eluting with Hexane: Ethyl acetate, 3:1), to give the desired *cis* and *trans* alkenes **40** as a pale yellow oil (9.4 g, 52.9% yield).

Data for compound **40**: ^{1}H NMR (400 MHz, $CDCl_3$); *cis* isomer: 7.64 (d, 2H, J = 7.7), 7.55 (d, 2H, J = 8.2), 7.48 (d, 2H, J = 7.7), 7.40 (d, 2H, J = 8.5), 7.10 (s, 2H), 5.08 (t, 1H, J = 9.6), 3.6 (d, 2H, J = 9.6), 1.5 (s, 9H); *trans* isomer: 7.55 (d, 2H, J = 8.2), 7.35 (d, 2H, J = 8.5), 7.28 (d, 2H, J = 8.0), 7.10 (d, 2H, J = 8.2), 6.63 (d, 1H, J = 12.0), 6.57 (d, 1H, J = 12.0), 5.08 (t, 1H, J = 9.6), 3.60 (d, 2H, J = 9.9), 1.50 (s, 9H).

Preparation of epoxide **41**:

The alkene **40** (9.4 g, 22 mmol) was dissolved in DCM (100 mL) and then mCPBA (5 g, 22 mmol, (purity 57-86%)) in DCM (100 mL) was added. The reaction was stirred at 40^{0}C for 10 hours then treated with 10% sodium sulfite until testing with starch paper was negative. The reaction mixture was then extracted with DCM. The combined organic extracts were washed with saturated sodium bicarbonate, brine and dried over anhydrous sodium sulfate. The product was concentrated to dryness. The product was purified *via* flash chromatography eluting with hexane:ethyl acetate (8:1 then 6:1). The desired epoxide **41** was obtained as a pale yellow foam (8.9 g, 91% yield).

Data for compound **41**: ^{1}H NMR (400 MHz, $CDCl_3$); mixture of isomers 7.47 (m, 2H), 7.27 (m, 2H), 7.17 (m, 2H), 7.01 (m, 2H), 4.97 (m, 1H), 4.35 (m, 2H), 3.49 (m, 2H), 1.48 (s, 9H).

Opening of epoxide **41** to give diol **42**:

The epoxide **41** (10.8 g) was dissolved in THF (15 mL). The solution was cooled in an ice bath, and formic acid (30 mL) was added slowly followed by water (0.5 mL). The reaction was stirred at 0 °C for 5 hours. On completion, the reaction was concentrated *in vacuo*. The residue was dissolved in THF (40 mL) and treated with 1N NaOH (aq.) until a color change was observed (yellow to brown). The reaction was monitored carefully by tlc. On completion, the product was extracted into ethyl acetate (200 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by column chromatography, eluting with 30% EtOAc in Hexane, to

give the desired diol **42** (7.2 g, 64%).

Data for compound **42**: ^1H NMR (400 MHz, $CDCl_3$); mixture of isomers (appears as two) 7.56 (d, 2H, J = 8.0), 7.52 (d, 2H, J = 8.0), 7.38 (d, 2H, J = 8.0), 7.35 (d, 2H, J = 8.0), 7.19 (d, 2H, J = 8.0), 7.12 (d, 2H, J = 8.0), 7.03 (d, 2H, J = 8.0), 6.96 (d, 2H, J = 8.0), 5.1-4.95 (m, 1H), 4.90-4.80 (m, 3H), 4.70-4.55 (m, 2H), 3.60-3.49 (m, 4H), 1.50 (s, 18H).

Oxidation of diol **42** to give dione **43**:

The diol **42** (1 g, 2.16 mmol) was dissolved in dichloromethane (12 mL). To this mixture was added 0.7M NaBr (1.47 mL, 1.03 mmol), and TEMPO (4 mg, 0.025 mmol) and the reaction mixture cooled to 0 °C. A freshly prepared buffered bleach solution (270 mg, $NaHCO_3$ dissolved in 16 mL bleach (5.25% sodium hypochlorite aq.)) was added dropwise to the reaction mixture. The reaction mixture was then stirred for a further 15 min. before work up. The reaction was quenched with 10% $Na_2S_2O_3$ aq. (30 mL), and extracted with ethyl acetate (3 x 60 mL). The combined organic layers were then washed with water (30 mL), brine (40 mL), and dried ($MgSO_4$) and concentrated *in vacuo*, to afford the dione **43** (841 mg, quantitative), as a pale yellow solid.

Data for compound **43**: ^1H NMR (400 MHz, $CDCl_3$); 8.01 (d, 2H, J = 8.5), 7.86 (d, 2H, J = 8.2), 7.83 (d,1H, J = 8.0), 7.69 (d, 2H, J = 8.2), 5.12 (t, 1H, J = 9.3), 3.62 (d, 2H, J = 9.4), 1.51 (s, 9H).

This solid can be then treated with 50 % TFA in DCM to afford the free

acid **43a** in quantitative yield.

Data for compound **43a**: ^{1}H NMR (300 MHz, DMSO-d_6); 8.0 (d, 2H), 7.92 (m, 6H), 5.24 (m, 1H), 3.80-3.65 (m, 2H).

General Method 4: **Synthesis of dione 54 *via* Wittig reacton** (Scheme 10)

A Wittig reaction following the same procedure as outlined in General Method 3, using Wittig reagent **39** (25 g, 49 mmol) in dry THF (300 mL), with 1M potassium *tert*-butoxide in THF (49 mL, 49 mmol) and 4-hydroxy benzaldehyde **48** (5.4 g, 44 mmol) gave the alkene **49** as a yellow solid (10.3 g, 85%).

The alkene **49** (8.7 g, 31.6 mmol) and t-butyl bromoacetate **50** (4.9 mL, 33.2 mmol) was dissolved in DMF (80 mL) and then Cs_2CO_3 (11.3 g, 34.8 mmol) was added. The reaction was stirred at R.T. for 16 hours. Upon completion, the reaction mixture was extracted with ethyl acetate (500 mL) and washed with water, 1 N NaOH, water, 10% citric acid, water and dried over anhydrous magnesium sulfate. The product was concentrated to dryness to obtain the derivatized alkene **51** as a white solid (15.8g, >99% crude yield) which was used without further purification in subsequent steps.

Data for compound **51**. ^{1}H NMR (400MHz: $CDCl_3$); cis isomer: 7.31 (d, 2H, J = 8.4), 7.13 (d, 2H J = 8.4), 7.09 (d, 2H, J = 8.4), 7.73 (d, 2H, J = 8.8) 6.53 (d, 1H, J = 12.0), 6.40 (d, 1H, J = 12.0), 4.47 (s, 2H), 1.46 (s, 9H). ^{1}H NMR (300MHz: $CDCl_3$); trans isomer:

7.44 (d, 2H, J = 8.4), 7.42 (d, 2H, J = 8.4), 7.33 (d, 2H, J = 8.4), 7.02 (d, 1H, J = 16.2), 6.89 (d, 1H, J = 15.6), 6.87 (d, 2H, J = 8.7), 4.52 (s, 2H), 1.47 (s, 9H).

Preparation of intermediate **52**:

The alkene **51** (3.7 g, 9.5 mmol) was dissolved in DCM (50 mL) and then mCPBA (4.3 g, purity 57-86%.) was added. The reaction was stirred at 40^{0}C for 8 hours then treated with 10% sodium sulfite until testing with starch paper was negative. The reaction mixture was then extracted with DCM. The combined organic extracts were washed with saturated sodium bicarbonate, brine and dried over anhydrous sodium sulfate. The product was concentrated to dryness to obtain the benzoate ester precursor **52** as a yellow foam (12.6g, >99% crude yield) and was used without further purification in subsequent steps.

Data for intermediate **52**: ^{1}H NMR (300MHz: $CDCl_3$); mixture of isomers: 8.03-7.83 (m, 2H), 7.56-7.51 (m, 1H), 7.42-7.32 (m, 3H), 7.24-7.00(m, 4H), 6.86-6.74 (m, 2H), 6.04-5.97 (m, 1H), 5.06-5.00 (m, 1H), 4.48-4.44 (m, 2H), 1.46-1.44 (m, 9H).

Removal of the benzoate ester of **52** to give diol **53**:

The benzoate ester **52** (5.3 g, 10.9 mmol) was dissolved in methanol (50 mL). The solution was cooled in an ice bath, and K_2CO_3 (6.5 g) followed by 5mL DI water were added. The reaction was stirred at 0 °C for 30 minutes. On completion, the product was extracted into ethyl acetate (200mL), wash with saturated NH_4Cl, water, brine, dried under $MgSO_4$ and

concentrated *in vacuo* to give a brownish residue. The product was purified by column chromatography, eluting with 20% EtOAc in Hexane, to give the desired diol **53** (3.5 g, 88%) as a light yellow oil.

Data for compound **53**: ^1H NMR (300MHz: $CDCl_3$); mixture of isomers: 7.45-7.32 (m, 2H), 7.16-6.95 (m, 4H), 6.87-6.75 (m, 2H), 4.82-4.57 (m, 2H), 4.52-4.50 (m, 2H), 1.46-1.44 (m, 9H).

Oxidation of diol **53** to give dione **54**:

The diol **53** (3.5 g, 8.3 mmol) was dissolved in dichloromethane (40 mL). To this mixture was added 0.7M NaBr (7 mL, 1.0 mmol, 0.5 eq,), and TEMPO (16.5 mg, 0.11 mmol, 0.01 eq) and the reaction mixture cooled to 0 °C. A freshly prepared buffered bleach solution (1.2 g, $NaHCO_3$ dissolved in 70 mL bleach (5.25% sodium hypochlorite aq.)) was added dropwise to the reaction mixture. The reaction mixture was then stirred for a further 15 min. before work up. The reaction was quenched with 10% $Na_2S_2O_3$ aq. (200 mL), and extracted with dichloromethane (250 mL). The organic layers was then washed with brine (150 mL), and dried ($MgSO_4$) and concentrated *in vacuo*, to afford the dione **54** (3.3g, quantitative), as a dark yellow oil.

Compound **54**: ^1H NMR (300MHz: $CDCl_3$); 7.96 (d, 2H, J = 9.0), 7.85 (d, 2H, J = 9.0), 7.67 (d, 2H, J = 8.7), 6.98 (d, 2H, J = 9.0), 4.61 (s, 2H), 1.49 (s, 9H).

General Method 5: **Heck Reaction on dione 24 to give dione 25** (Scheme 6)

The dione **24** (1 equiv.) was dissolved in DMF (to make 0.14M solution), followed by addition of $Pd(OAc)_2$ (0.02 equiv.), TEA (3 equiv.), (*o*-

Tolyl)$_3$P (0.09 equiv.), and acrylic acid (or acrylamide) (1.2 equiv.). The reaction mixture was heated to 100 °C for 2 hours. The reaction was then quenched *via* addition of water and extraction with methylene chloride. The combined organic layers were washed with 1N HCl (aq.), water, dried (Na_2SO_4), and concentrated *in vacuo*, to give the desired derivatized dione **25** (90% crude yield). This dione was used for subsequent reactions without further purification.

General Method 6: **Coupling of amine 26 to dione acid 25 to give amide 27** (Scheme 6)

The dione **25** (1.0 equiv.) was suspended in $CHCl_3$ (to make 0.55M solution). EDCI (1.3 equiv.), HOBt (1.3 equiv.), and TEA (2.0 equiv.), were then added (mixture goes clear on addition of base) and stirred at room temperature for 1 hour. The amine **26** (1.2 equiv.) was then added and the reaction stirred overnight at room temperature. The reaction was then worked up *via* addition of water and extraction with methylene chloride. The combined organic layers were washed with 1N HCl (aq.), water, dried ($MgSO_4$), and concentrated *in vacuo*. The product was then purified *via* flash chromatography.

General Method 7: **Synthesis of Imidazole Core** (Scheme 6)

Acetic acid (20 mL) was added to a mixture of the dione **27** (1.0 equiv.), aldehyde (1.5 equiv.) and NH_4OAc (30 equiv.), and heated to 100 °C for ~ 2 hours. The reaction has to be monitored carefully if t-butyl groups are present, as these will be removed with prolonged heating. The reaction

mixture was extracted with ethyl acetate and washed with water, then back extract with ethyl acetate. The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The imidazole was purified by flash column chromatography eluting with hexane/ethyl acetate (3:1). The compound fluoresces as a yellow spot on TLC under long wave UV lamp. The desired imidazole is obtained as a yellow or white solid.

General Method 8: **Protocol for synthesis of imidazoles 58 and 60 *via* the Heck reaction** (Scheme 11)

The Br imidazole **55** or **56** (1 equiv.) was dissolved in DMF (0.5-1.0M), followed by addition of $Pd(OAc)_2$ (0.2 equiv.), TEA (2 equiv.), (o-Tolyl)$_3$P (0.4 equiv.), and an acrylamide **57** (1.2 equiv.). The reaction mixture was heated to 100 °C for 1-2 hours. The reaction was then quenched *via* addition of water, (acidified to pH 1-2 with 1N HCl if starting from Br imidazole **56**) and extracted with ethyl acetate (2x). The combined organic layers were washed with water and brine, dried with ($MgSO_4$), and concentrated *in vacuo* to give a yellow oil. The crude was purified by column chromatography, eluting with hexane/ethyl acetate (methanol in dichloromethane with 1% formic acid if from **56**), to give the desired imidazole. The purified compound was then recrystallized to give the desired compound as a yellow solid.

General Method 9: **Synthesis of Acrylamide 57** (Scheme 12).

Acrylamides **57** were prepared by adding acryloyl chloride (1 equiv.) to a cooled solution (0 °C) of the desired amine **45** (1.0 equiv.) in dichloromethane (0.5M) with triethylamine (1.0 equiv.) as base. These

acrylamides were used directly, without purification in the Heck reaction (Scheme 11 for example).

General Method 10: **Hydrolyses of a methyl or ethyl ester**

A mixture of ethyl or methyl ester (1 equiv.), 1N LiOH (15 equiv.), and 1,4-Dioxane (0.3 M of ethyl ester) was stirred at rt. overnight. The reaction mixture was acidified with 1N HCl and extracted with ethyl acetate. The ethyl acetate solution was washed with water and brine, dried over $MgSO_4$ and concentrated to dryness. The final acid was recrystallized using isopropyl alcohol and ethyl acetate.

General Method 11: **Hydrolyses of a t-butyl ester**

The *t*-Butyl ester was dissolved in 50% TFA dichloromethane solution with ice bath. The reaction stirred at 0 °C for ~1 hour. The reaction mixture was then concentrated *in vacuo*. The product was precipitated with a mixture of acetonitrile (few drops) and ether, and collected *via* filtration. This product can be recrystallized from methanol/ethyl acetate.

General Method 12: **Synthesis of dione 115 *via* condensation of two aldehydes 112 and 113** (Scheme 18)

Methyl 4-formylcinnamate **113** (5 g, 0.026 moles) and t-butyl 4-formylcinnamate **112** (3 g, 0.013 moles) were dissolved in dry THF (70 mL). Pyridine (6 mL) was then added followed by $TiCl_3$ (1.0 M in DCM/THF, 95 mL, 0.091moles). The reaction was allowed to stir for 1 hour at ambient then 18 hours at -20 °C. Additional $TiCl_3$ (1.0 M in DCM/THF, 20 mL) was added and the reaction stirred at ambient temperature for a further 5 hours.

The reaction was then concentrated *in vacuo* by to remove approximately 60% of the solvent, then quenched *via* addition of sat. $NaHCO_3$. The mixture is then filtered through celite and the resulting solution extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were then washed with brine and concentrated *in vacuo*. The desired product was then purified *via* column chromatography eluting with a gradient of ethyl acetate in hexane (20-40%). To give the desired diol **114** (1.5g, 24.7%).

Data for compound **114**:

^{1}H-NMR (300 MHz, $CDCl_3$): 7.51 (d, 2H, J = 8.4), 7.49 (d, 1H, J = 15.6), 7.35 (d, 2H, J = 8.1), 7.14-7.08 (m, 4H), 6.30 (d, 1H, J = 15.9), 5.20-5.14 (m, 1H), 4.69 (br, t, 2H, J = 9.7), 3.82 (s, 3H), 3.61-3.58 (m, 2H), 3.19 (d, 2H, J = 18), 1.52 (s, 9H).

Oxidation of diol **114** to give dione **115**:

The diol **114** (1.5 g, 3.21 mmoles) was dissolved in dichloromethane (10 mL). To this mixture was added 0.7 M NaBr (2.18 mL, 1.53 mmoles), TEMPO (5.9 mg, 0.037 mmoles) and the reaction mixture cooled to 0 °C. A freshly prepared buffer bleach solution (401 mg, $NaHCO_3$ dissoved in 24 mL bleach (5.25% sodium hydrochlorite aq.) was added dropwise to the reaction mixture was then srirred for futher 15 min. before work up. The reaction was quenched with 10% $Na_2S_2O_3$ aq. (44 mL), and extracted with ethyl acetate (3 X 80 mL). The combined organic layers were then washed with water (40 mL), and brine (50 mL), and dried ($MgSO_4$) and concentrated in *vacuo*, to afford the dione **115** (1.5 g, quantitative), as a pale yellow solid.

Data for compound **115**:

^{1}H-NMR (300 MHz, $CDCl_3$): 8.03 (d, 2H, J = 8.7), 7.99 (d, 2H, J = 8.1), 7.83 (d, 2H, J = 8.7), 7.64 (d, 2H, J = 8.4), 7.60 (d, 1H, J = 16.0), 6.49 (d, 1H, J = 15.9), 5.31-5.23 (m, 1H), 4.03 (s, 3H), 3.70-3.65 (m, 2H), 1.54 (s, 9H).

General Method 13: **Synthesis of keto-bromide intermediate 130 (where R^1 = Et) (Scheme 20)**

4-Bromobenzyl-4-methoxyphenylketone 127

To a mixture of *p*-bromo-phenylacetic acid **126** (51g, 237 mmol, 1 equiv.), and $SOCl_2$ (35 mL, 480 mmol, 2 equiv.), was added 1 drop of DMF. The mixture was stirred at 60°C for 30 min. then concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (140 mL), and $AlCl_3$ (35 g, 262 mmol, 1.1 equiv.) was added to the solution portionwise at 0° C. To this mixture was added anisole (30 g, 277 mmol, 1.2 equiv.) dropwise at 0° C, and the mixture stirred at 0° C for 15 min and r.t. for 1 h. The reaction mixture was poured onto ice-water, and extracted with $CHCl_3$ (3 x 150 mL). The combined extracts were washed with sat. $NaHCO_{3\,(aq.)}$ (2 x 200 mL), and water (3 x 200 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was suspended in hexane, and the insoluble material collected by filtration to give *4-Bromobenzyl-4-methoxyphenylketone* **127** 65g (90%).

Data for Compound **127**: ^{1}H-NMR (300 MHz, $CDCl_3$): 7.98 (d, 2H, J = 9.0), 7.45 (d, 2H, J = 8.4), 7.15 (d, 2H, J = 8.4), 6.94 (d, 2H, J = 9.0), 4.20 (s, 2H), 3.88 (s, 3H).

4-Bromobenzyl-4-hydoxyphenylketone 128

A mixture of 4-Bromobenzyl-4-methyloxyphenylketone **127** (65 g, 213 mmol), LiI (50 g, 374 mmol) and collidine (100 mL) was stirred at 180° C for

3 h. The reaction mixture was diluted with ethylene glycol (100 mL) and stirred at 180 ° C for 30 min. The mixture was cooled, acidified to pH 1 with dilute (1N) HCl, and extracted with EtOAc (3 x 150 mL).. The combined extracts were washed with water (3 x 200 mL), Sat. $NaHCO_3$ (200 mL), and brine (3 x 200 mL), successively, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was recrystallized using EtOAc to give *4-Bromobenzyl-4-hydoxyphenylketone* **128** 50 g (81%).

Data for compound **128**: ^{1}H-NMR (300 MHz, $CDCl_3$): 7.93 (d, 2H, J = 8.7), 7.50 (d, 2H, J = 8.4), 7.41 (d, 2H, J = 8.7), 6.89 (d, 2H, J = 9.0), 6.29 (s, 2H).

4-[4-Bromophenylacetyl]phenoxyacetic ethyl ester (R^1 = Et) 129

A mixture of 4-Bromobenzyl-4-hydoxyphenylketone **128** (50 g, 172 mmol, 1.0 equiv.), ethyl bromoacetate (30 g, 180 mmol, 1.05 equiv.), Cs_2CO_3 (60 g, 184 mmol, 1.07 equiv.) and DMF (300 mL) was stirred at r.t .for 1 hr. The reaction mixture was diluted with water (200 mL), and the resulting solid was collected by filtration. The solid was recrystallized from EtOH to give *4-[4-Bromophenylacetyl]phenoxyacetic ethyl ester (R^1 = Et)* **129** 53 g (82%).

Data for Compound **129**: ^{1}H-NMR (300 MHz, $CDCl_3$): 7.98 (d, 2H, J = 9.3), 7.45 (d, 2H, J = 8.1), 7.13 (d, 2H, J = 8.4), 6.95 (d, 2H, J = 9.0), 4.69 (s, 2H), 4.29 (q, 2H, J = 7.2), 4.19 (s, 2H), 1.31 (t, 3H, J = 7.2).

{4[Bromo-(4-bromophenyl) acetyl] phenoxy} acetic acid ethyl ester 130

To a mixture of 4-[(4-bromophenyl)acetyl]phenoxyacetic acid ethyl ester **129** (52 g, 136 mmol) and $CHCl_3$ (400 mL) was added Br_2 (7.5 mL) dropwise at 40° C, and the mixture was stirred at r.t. for 1 h. The reaction

mixture was washed with Sat. $NaHCO_{3\,(aq)}$ (2x 200 mL) and water (3 x 200 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The desire product was recrystallized using ethyl acetate and hexane to give *{4[Bromo-(4-bromophenyl) acetyl] phenoxy} acetic acid ethyl ester* **130** 56 g (90%). Data for compound **130**; ^{1}H-NMR (300 MHz, $CDCl_3$): 7.98 (d, 2H, J = 9.0), 7.50 (d, 2H, J = 8.4), 7.41 (d, 2H, J = 8.4), 6.94 (d, 2H, J = 8.7), 6.26 (s, 2H), 4.69 (s, 2H), 4.28 (q, 2H, J = 7.2), 1.30 (t, 3H, J = 7.2).

General Method 14: **Reduction of double bonds using 10% Pd/C under H_2.** (Scheme 24)

The compound is dissolved in ethyl acetate (with 10% methanol if necessary for dissolution) (to give ~0.1M solution). 10% Pd/C is added (10 - 20 wt %). The reaction is stirred under an atmosphere of H_2 gas at ambient pressure for ~1 hour. The catalyst is removed *via* filtration through celite. The resulting compound is purified *via* recrystallization.

General Method 15: **Synthesis of dione 123** (Scheme 19)

To 4,4'-dibromobenzil **120** (5 g, 14 mmol, 1 equiv.) in DMF (28 mL, 0.5M) was added $Pd(OAc)_2$ (94 mg, 0.42 mmol, 0.03 equiv.), P(o-tolyl)$_3$ (511 mg, 1.7 mmol, 0.12 equiv.), TEA (3.9 mL, 28 mmol, 2 equiv.), and t-butyl acrylate (2.9 mL, 20 mmol, 1.45 equiv.). The reaction was stirred at 100 C for 1h. After, the acrylamide **57i** (2.21 g, 7.5 mmol, 0.55 equiv.) was added and the mixture stirred an additional hour. Upon completion, the mixture was diluted with ethyl acetate. The mixture was extracted with ethyl acetate (400 mL), washed with water (200 mL). The aqueous layer was back extracted

with an additional 250 mL ethyl acetate. The combine organic phase was washed with water, dried ($MgSO_4$), filtered and concentrated *in vacuo* to obtain a brown oil. The oil was purified by flash column chromatography eluting with a hexane/ethyl acetate/dichloromethane mixture to afford the desired product ($R^{2'} = C_{12}H_{25}$) as a light brown solid (1.8 g, 39%).

Data for **123a** ($R^{2'} = C_{12}H_{25}$): ^{1}H-NMR (400 MHz, $CDCl_3$): 7.98 (d, 2H, J = 6.3), 7.97 (d, 2H, J = 6.0), 7.61-7.58 (m, 6H), 6.52 (d, 1H, J = 11.7), 6.49 (d, 1H, J = 12.0), 5.77 (t, 1H, J = 4.2), 3.39 (q, 2H, J = 5.4), 1.70 (brs, 2H), 1.59-1.54 (m, 9H), 1.33-1.30 (m, 18H), 0.88 (t, 3H, J = 5.1).

Data for **123b** ($R^{2'} = C_{16}H_{33}$): ^{1}H-NMR (300 MHz, $CDCl_3$): 7.98 (d, 4H, J = 7.2), 7.69-57 (m, 6H), 6.51 (d, 1H, J = 15.9), 6.49 (d, 1H, J = 15.9), 5.77 (brs, 1H), 3.39 (q, 2H, J = 5.4), 1.82 (brs, 2H), 1.52 (s, 9H), 1.29 (s, 26H), 0.90 (t, 3H, J = 5.1).

Data for **123c** ($R^{2'} = PhC_7H_{15}$): ^{1}H-NMR (300 MHz, $CDCl_3$): 8.44 (s, 1H), 7.97 (d, 2H, J = 8.7), 7.90 (d, 2H, J = 8.7), 7.71 (d, 1H, J = 15.9), 7.66-7.48 (m, 7H), 7.12 (d, 2H, J = 8.7), 6.77 (d, 1H, J = 15.9), 6.50 (d, 1H, J = 15.9), 2.50 (m, 2H), 1.50 (br s, 11H), 1.30 (br s ,4H), 0.88 (t, 3H, J = 6.9).

Data for **123d** ($R^{2'} = (C_6H_{13})_2$): ^{1}H-NMR (300 MHz, $CDCl_3$): 7.98 (d, 4H, J = 8.1), 7.70 (d, 1H, J = 15.3), 7.63 (d, 4H, J = 8.4), 7.59 (d, 1H, J = 16.0), 6.95 (d, 1H, J = 15.3), 6.48 (d, 1H, J = 16.2), 3.40 (br q, 4H, J = 8.1), 1.68-1.50 (m, 4H), 1.4-1.24 (m, 12H), 0.96-0.82 (m, 6H).

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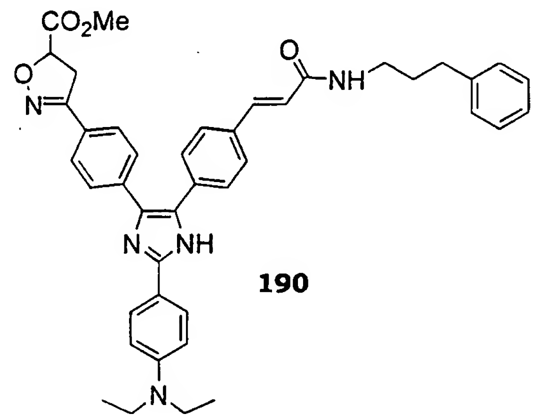
Example 1

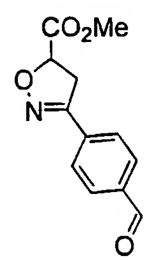
3-[4-(2-(4-Diethylamino-phenyl)-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester 190



190

Dione was synthesized according to *General Method 12* followed by *General Method 11* to give the free acid **44** (Using the methodology outlined in Scheme 18).

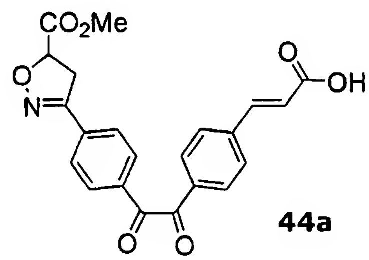
The aldehyde input **34b** was synthesized according to *General Method 1*, using methyl acrylate in place of *tert*-butyl acrylate to give aldehyde **34b** (R = Me) g, (92%).



34b

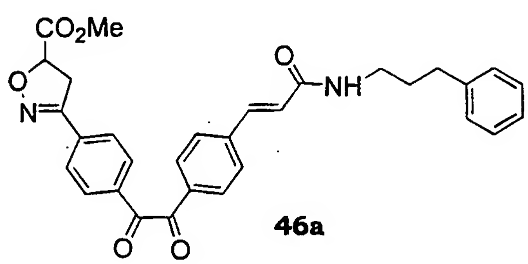
Data for aldehyde **34b**: ^{1}H-NMR (300 MHz, $CDCl_3$); mixture of isomers: 10.06 (s, 1H), 7.94 (d, 2H, J = 8.1), 7.86 (d, 2H, J = 8.4), 5.30-5.24 (m, 1H), 3.85 (s, 3H), 3.72-3.67 (m, 2H).

The t-butyl ester of dione **44** was converted to free acid **44b** *via* treatment of with 50% TFA dichloromethane solution with ice bath. After two hours, the reaction was dried by vacuum. This gave, after work-up, *3-(4-{2-[4-((E)-2-Carboxy-vinyl)-phenyl]-2-oxo-ethanoyl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester* **44b** ($R^{1'}$ = Me) (Quantitative).



44a

Data for Compound **44b**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.04-7.91 (m, 8H), 7.68 (d, 1H, J = 15.9), 6.74 (d, 1H, J = 15.9), 5.42-5.36 (m, 1H), 3.90-3.63 (m, 2H), 3.71 (s, 3H).



46a

3-[4-(2-Oxo-2-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-ethanoyl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester **46a** (Scheme 9) was synthesized according to *General Method 6* from dione **44b** (0.23 g, 0.57 mmol) in $CHCl_3$ (2 mL), EDCI (0.13 g, 0.69 mmol), HOBt (0.093 g, 0.69 mmol), DIEA (0.3 mL, 1.71 mmol), and 3-phenylpropylamine **26a** (0.098 mL, 0.69 mmol). After purification *via* column chromatography eluting with ethyl acetate:hexane the desired dione *3-[4-(2-Oxo-2-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-ethanoyl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester* **46a** was obtained (0.29 g, 97%).

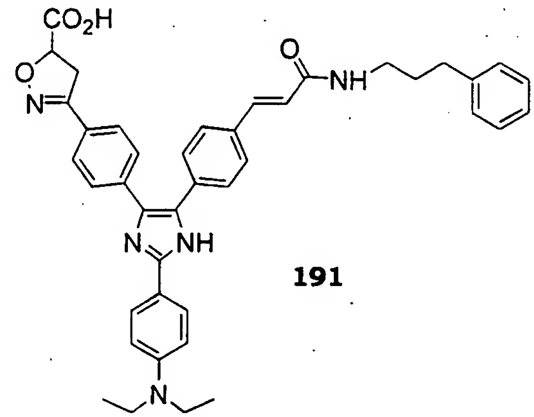
Data for *3-[4-(2-Oxo-2-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-ethanoyl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester* **46a**: ^{1}H-NMR (300 MHz, $CDCl_3$): 8.01 (d, 2H, J = 6.6), 7.96 (d, 2H, J = 8.1), 7.81 (d, 2H, J = 9.0), 7.65-7.52 (m, 3H), 7.35-7.14 (m, 5H), 6.44 (d, 1H, J = 15.6), 5.79 (t, 1H, J = 5.0), 5.26 (dd, 1H, J = 10.5, 7.2), 3.83 (s, 3H), 3.72-3.60 (m, 2H), 3.43 (q, 2H, J = 6.3), 2.70 (t, 2H, J = 7.5), 2.00-1.85 (m, 2H).

Compound **190** was synthesized according to *General Method 7* from dione **46a** (0.28 g, 0.53 mmol) in acetic acid (3 mL) with 4-diethylaminobenzaldehyde (0.1 g, 0.59 mmol) and NH_4OAc (1.23 g, 16 mmol). The resulting imidazole was purified by flash column chromatography eluting with hexane/ethyl acetate (3:1). The desired imidazole *3-[4-(2-(4-Diethylamino-phenyl)-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester* **190** was obtained as a yellow solid (0.16 g, 44%).

Data for *3-[4-(2-(4-Diethylamino-phenyl)-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester* **190**: ^{1}H-NMR (300 MHz, $CDCl_3$): 7.88 (br s, 2H), 7.50-7.05 (m, 15H), 6.67 (br s, 2H), 6.20 (br d, 1H, J = 14.8), 5.13 (dd, 1H, J = 10.0, 8.0), 3.77 (s, 3H), 3.62-3.50 (m, 2H), 3.50-3.20 (m, 6H), 2.58 (t, 2H, J = 7.6), 1.94-1.72 (m, 2H), 1.14 (t, 6H, J = 7.0).

Example 2

3-[4-(2-(4-Diethylamino-phenyl)-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid 191



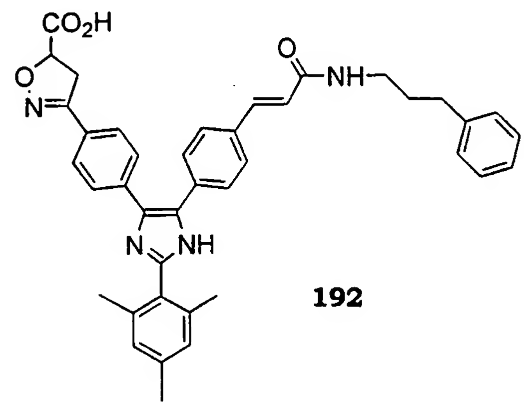
191

Imidazole **191** was synthesized according to *General Method 10 via* hydrolyses of the methyl ester of imidazole **190** (Example 1), according to *General Method 10* from imidazole **191** (methyl ester) (0.16 g, 0.23 mmol), 1N LiOH (3.5 mL, 3.5 mmol), and 1,4-Dioxane (3.5 mL). *3-[4-(2-(4-Diethylamino-phenyl)-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid* **191** was obtained, after recrystallization, as a pale yellow solid (0.11 g, 72%).

Data for *3-[4-(2-(4-diethylamino-phenyl)-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid* **191**: ^{1}H-NMR (300 MHz, CD_3OD): 7.86 (d, 2H, J = 9.3), 7.71 (d, 2H, J = 8.4), 7.61 (d, 2H, J = 8.4), 7.58-7.48 (m, 5H), 7.30-7.10 (m, 5H), 6.84 (d, 2H, J = 9.3), 6.64 (d, 1H, J = 15.9), 5.09 (dd, 1H, J = 11.4, 7.2), 3.69 (dd, 1H, J = 17.1, 11.7), 3.35 (dd, 1H, J = 18.0, 7.8), 3.49 (q, 4H, J = 6.9), 3.38-3.24 (m, 2H), 2.68 (t, 2H, J = 7.7), 1.90-1.80 (m, 2H), 1.22 (t, 6H, J = 7.1); MS (APcI): 668.0 (100, [M]), 669.3 (38, [M+H]); calcd $C_{41}H_{41}N_5O_4$ ([M]) 667.8.

Example 3

3-{4-[5-{4-[(E)-2-(3-Phenyl-propylcarbamoyl)-vinyl]-phenyl}-2-(2,4,6-trimethyl-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid 192



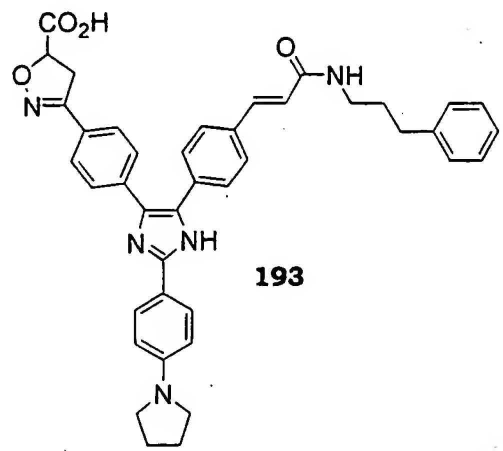
192

Compound **192** was synthesized according to *General Method 7* from dione **46a** (0.5 g, 0.88 mmol) in acetic acid (1 mL), with 2,4,6-trimethylbenzaldehyde (0.26 g, 1.76 mmol) and NH_4OAc (2.0 g, 26.4 mmol), which gives 3-{4-[5-{4-[(E)-2-(3-Phenyl-propylcarbamoyl)-vinyl]-phenyl}-2-(2,4,6-trimethyl-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester. The methyl ester was hydrolyzed according to *General Method 10* to give, after recrystallization, the desired imidazole *3-{4-[5-{4-[(E)-2-(3-Phenyl-propylcarbamoyl)-vinyl]-phenyl}-2-(2,4,6-trimethyl-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid* **192** as a yellow solid (0.28 g, 50%).

Data for *3-{4-[5-{4-[(E)-2-(3-Phenyl-propylcarbamoyl)-vinyl]-phenyl}-2-(2,4,6-trimethyl-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid* **192**: MS (APcI): 639.5 (100, [M+H]); calcd $C_{40}H_{38}N_4O_4$ ([M+H]) 639.8.

Example 4

3-{4-[5-{4-[(E)-2-(3-Phenyl-propylcarbamoyl)-vinyl]-phenyl}-2-(4-pyrrolidin-1-yl-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid 193



193

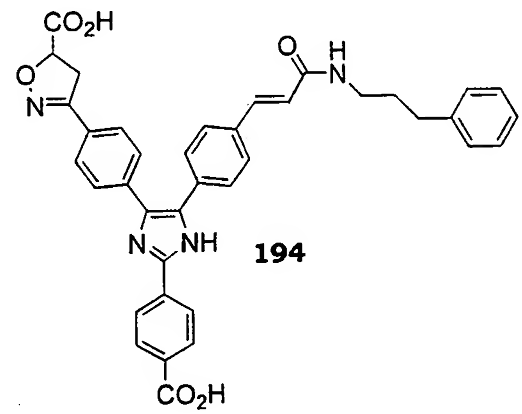
Compound **193** was synthesized according to *General Method 7* from dione **46a** (0.2 g, 0.35 mmol) in acetic acid (2 mL), with 4-pyrrolidin-1-yl-benzaldehyde (0.07 g, 0.38 mmol) and NH_4OAc (0.8 g, 10.5 mmol), which gives 3-{4-[5-{4-[(E)-2-(3-Phenyl-propylcarbamoyl)-vinyl]-phenyl}-2-(4-pyrrolidin-1-yl-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester. The methyl ester was hydrolyzed according to *General Method 10* to give, after recrystallization, the desired imidazole *3-{4-[5-{4-[(E)-2-(3-Phenyl-propylcarbamoyl)-vinyl]-phenyl}-2-(4-pyrrolidin-1-yl-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid* **193** as a yellow solid (0.078 g, 33%).

Data for *3-{4-[5-{4-[(E)-2-(3-Phenyl-propylcarbamoyl)-vinyl]-phenyl}-2-(4-pyrrolidin-1-yl-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid* **193**: ^{1}H-NMR (300 MHz, DMSO): 8.16 (t, 1H, J = 5.4), 7.90 (d, 2H, J = 9.0), 7.70-7.56 (m, 8H), 7.43 (d, 1H, J = 15.9), 7.32-7.18 (m, 5H),

6.67-6.61 (m, 3H), 5.17 (dd, 1H, J = 11.4, J = 6.9), 3.79-3.55 (m, 2H), 3.35 (br s, 4H), 3.23-3.16 (m, 2H), 2.62 (t, 2H, J = 7.8), 1.98 (br s, 4H), 1.81-1.72 (m, 2H). MS (ESI): 666.7 (100, [M+H]); calcd $C_{41}H_{40}N_5O_4$ ([M+H]) 666.3.

Example 5

3-[4-(2-(4-Carboxy-phenyl)-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid 194



194

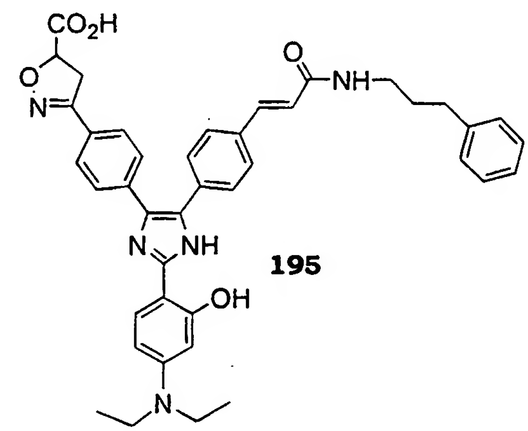
Compound **194** was synthesized according to *General Method 7* from dione **46a** (0.2 g, 0.35 mmol) in acetic acid (2 mL), 4-formylbenzoic acid (0.08 g, 0.53 mmol) and NH_4OAc (0.82 g, 10.6 mmol), which gives 3-[4-(2-(4-Carboxy-phenyl)-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester. The methyl ester was hydrolyzed according to *General Method 10* to give, after recrystallization, the desired imidazole *3-[4-(2-(4-Carboxy-phenyl)-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid* **194** as a yellow solid (0.1 g, 45%).

Data for *3-[4-(2-(4-Carboxy-phenyl)-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic*

acid **194**: ^{1}H-NMR (300 MHz, DMSO): 8.22 (d, 2H, J = 8.7), 8.16 (br s, 1H), 8.05 (d, 2H, J = 8.7), 7.80-7.56 (m, 8H), 7.45 (d, 1H, J = 16.0), 7.32-7.16 (m, 5H), 6.67 (d, 1H, J = 16.0), 5.19 (br t, 1H, J =8.7), 3.80-3.54 (m, 2H), 3.20 (dd, 2H, J = 12.6, 6.6), 2.62 (t, 2H, J = 7.7), 1.82-1.72 (m, 2H). MS (APcI): 641.3 (30, [M+H]), 553.3 (100); calcd $C_{38}H_{33}N_4O_6$ ([M+H]) 641.24.

Example 6

3-[4-(2-(4-Diethylamino-2-hydroxy-phenyl)-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid 195



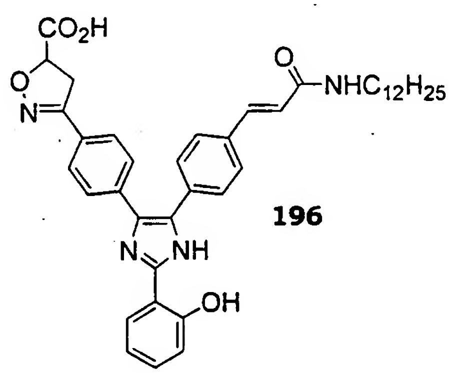
195

Compound **195** was synthesized according to *General Method 7* from dione **46a** (0.2 g, 0.35 mmol) in acetic acid (2 mL), 2-hydroxy-4-diethylamino-benzaldehyde (0.1 g, 0.53 mmol) and NH_4OAc (0.82 g, 10.59 mmol), which gives of 3-[4-(2-(4-Diethylamino-2-hydroxy-phenyl)-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester. The methyl ester was hydrolyzed according to *General Method 10* to give, after recrystallization, the desired imidazole *3-[4-(2-(4-Diethylamino-2-hydroxy-phenyl)-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid* **195** as a yellow solid (0.1 g, 41.8%).

Data for *3-[4-(2-(4-Diethylamino-2-hydroxy-phenyl)-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid* **195**: MS (ESI): 314.5 (100), 684.6 (54, [M+H]); calcd $C_{41}H_{41}N_5O_5$ ([M+H]) 684.8.

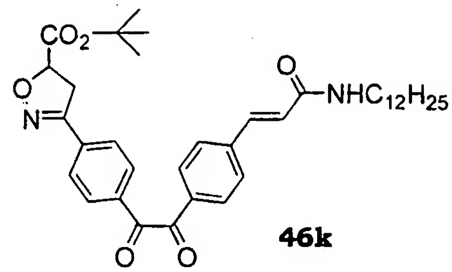
Example 7

3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-(2-hydroxy-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid 196



196

3-(4-{2-[4-((E)-2-Carboxy-vinyl)-phenyl]-2-oxo-ethanoyl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester **44a** ($R^{1'}$ = *tert*-Bu, Scheme 9) was synthesized according to *General Method 5* from dione **43a** (**43a** - synthesized *via General Method 3*). Dione ***46b*** (Scheme 9) was synthesized according to *General Method 6* from dione **44a** (1.5 g, 3.3 mmol) in $CHCl_3$ (15 mL), EDCI (0.96 g, 5.0 mmol), HOBt (0.68 g, 5.0 mmol), DIEA (1.08 mL, 8.3 mmol), and dodecylamine **26b** (0.93 g, 5.0 mmol). After purification *via* column chromatography eluting with ethyl acetate:hexane the desired *dione 3-(4-{2-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-oxo-ethanoyl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* ***46b*** was obtained (1.52 g, 75%).



46k

Data for *dione 3-(4-{2-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-oxo-ethanoyl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* ***46b***: ^{1}H-NMR (300 MHz, $CDCl_3$): 8.01 (d, 2H, J = 8.4), 7.96 (d, 2H, J = 8.4), 7.82 (d, 2H, J = 8.4), 7.64 (d, 1H, J = 15.6), 7.61 (d, 2H, J = 8.1), 6.53 (d, 1H, J = 15.6), 5.86 (brt, 1H, J = 5.7), 5.14-5.08 (m, 1H), 3.61-3.58 (m, 2H), 3.42-3.35 (m, 2H), 1.51 (brs, 11H), 1.26 (brs, 18H), 0.88 (t, 3H, J = 6.7).

Compound **196** was synthesized according to *General Method 7* from dione ***46b*** (0.2 g, 0.32 mmol) in acetic acid (3 mL) with 2-hydroxy-benzaldehyde (0.06 g, 0.53 mmol) and NH_4OAc (0.8 g, 9.6 mmol), which gives 3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-(2-hydroxy-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester. The *tert*-butyl ester was hydrolyzed according to *General Method 11* to give, after recrystallization *3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-(2-hydroxy-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid* **196** as a yellow solid (0.1 g, 47%).

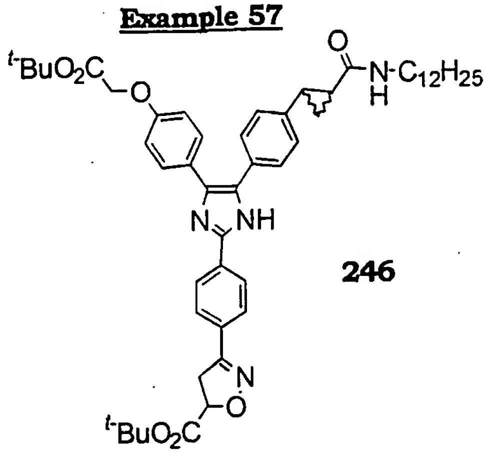
Data for *3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-(2-hydroxy-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid* **196**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.10 (t, 1H, J = 5.4), 8.03 (d, 1H, J =7.2), 7.76 (d, 2H, J = 8.1), 7.66-7.55 (m, 6H), 7.43 (d, 1H, J = 15.6), 7.32 (t, 1H, J = 7.6), 7.01 (d, 1H, J = 7.5), 6.98 (t, 1H, J = 7.8), 6.65 (d, 1H, J = 15.6), 5.19

(dd, 1H, J = 11.4, 6.9), 3.80-3.56 (m, 2H), 3.20-3.13 (m, 2H), 1.50-1.40 (m, 2H), 1.24 (br s, 18H), 0.84 (t, 3H, J = 6.7). MS (ESI): 663.6 (100, [M+H]); calcd $C_{40}H_{46}N_4O_5$ ([M+H]) 663.4.

Example 8

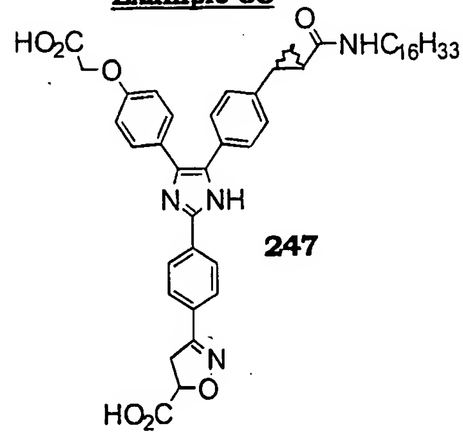
3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid 197

Example 57



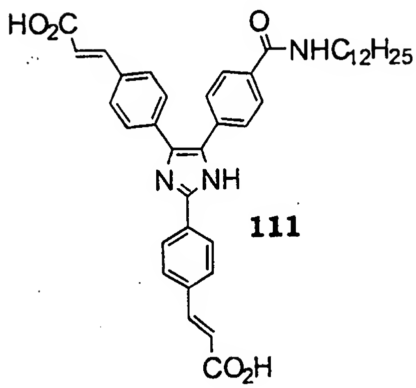
246

Example 58



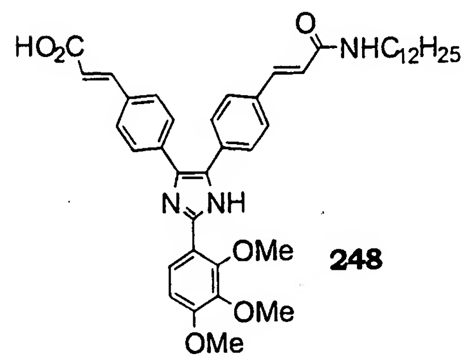
247

Example 59



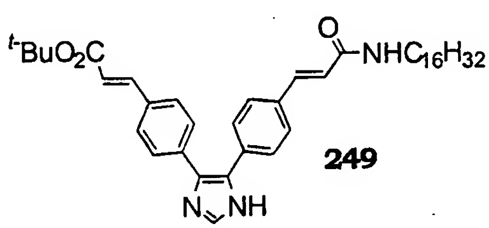
111

Example 60



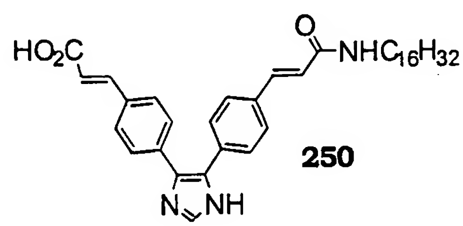
248

Example 61



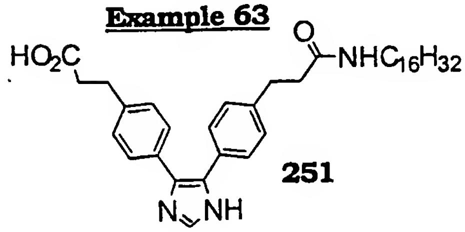
249

Example 62



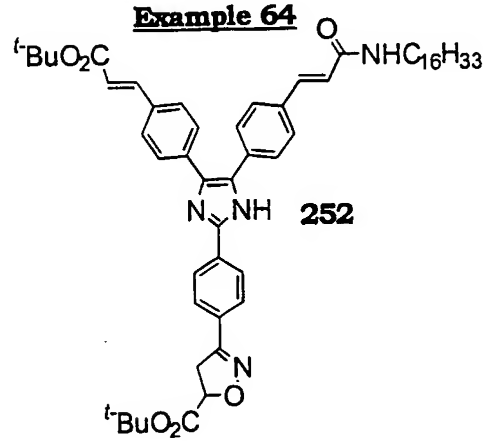
250

Example 63



251

Example 64



252

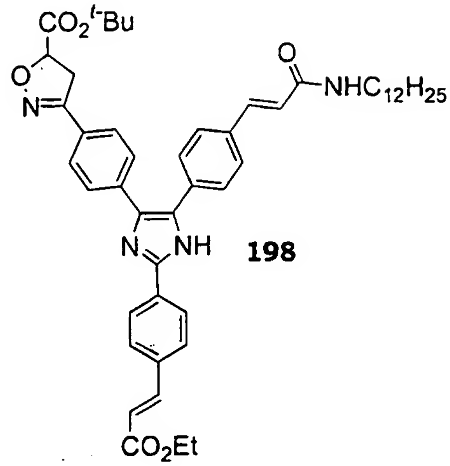
Compound **197** was synthesized according to *General Method 7* from dione ***46b*** (0.22 g, 0.36 mmol) in acetic acid (3 mL) hexamethyltetramine

(0.25 g, 1.78 mmol) and NH_4OAc (0.8 g, 10.7 mmol), which gives 3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester. The *tert*-butyl ester was hydrolyzed according to *General Method 11* to give, after recrystallization *3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid* **197** as a yellow solid (0.1 g, 48.7%).

Data for *3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid* **197**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.46 (br s, 1H), 8.10 (t, 1H, J = 5.4), 7.73 (d, 2H, J = 8.1), 7.60 (d, 2H, J = 8.4), 7.55 (d, 2H, J = 8.7), 7.49 (d, 2H, J = 8.1), 7.41 (d, 1H, J =15.6), 6.63 (d, 1H, J = 15.9), 5.19 (dd, 1H, J = 11.4, 6.6), 3.79-3.55 (m, 2H), 3.19-3.12 (m, 2H), 1.50-1.40 (m, 2H), 1.24 (br s, 18H), 0.84 (t, 3H, J = 6.3). MS (ESI): 571.6 (100, [M+H]), 428.5 (50), 279.5 (60); calcd $C_{34}H_{43}N_4O_4$ ([M+H]) 571.3.

Example 9

3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 198



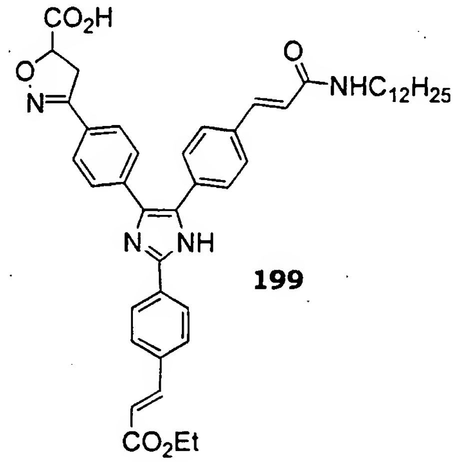
198

Compound **198** was synthesized according to *General Method 7* from dione ***46b*** (0.14 g, 0.22 mmol) in acetic acid (2 mL), 4-formylcinnamic acid ethyl ester (0.047 g, 0.23 mmol) and NH_4OAc (0.5 g, 6.6 mmol). The resulting imidazole was purified by flash column chromatography eluting with hexane/ethyl acetate (3:1). The desired imidazole *3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **198** was obtained as a yellow solid (0.07 g, 42.8%).

Data for *3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **198**: ^{1}H-NMR (300 MHz, DMSO-d$_6$): 8.14 (d, 2H, J = 8.4), 8.86 (d, 2H, J = 8.1), 7.74 (d, 1H, J = 15.9), 7.70-7.35 (m, 9H), 6.72 (d, 1H, J = 15.9), 6.60 (d, 1H, J = 15.9), 5.22-5.05 (m, 1H), 4.21 (q, 2H, J = 7.1), 3.85-3.67 (m, 1H), 3.67-3.46 (m, 1H), 3.22-3.10 (m, 2H), 1.78-1.45 (m, 2H), 1.55-1.35 (m, 11H), 1.48-1.10 (m, 21H), 0.85 (t, 3H, J = 6.6); MS (APcI): 657.4 (100), 801.2 (40, [M]); calcd $C_{49}H_{61}N_4O_6$ ([M]) 801.0.

Example 10

3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid 199



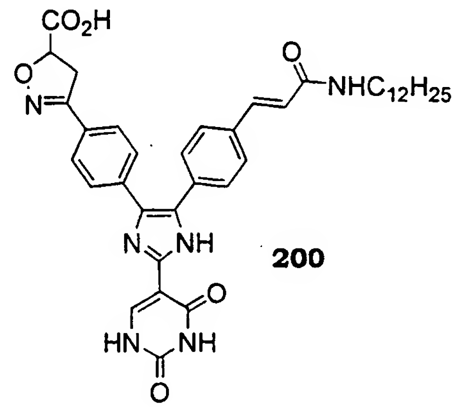
199

Imidazole **199** was synthesized according to *General Method 11 via* hydrolyses of the *tert*-butyl ester of imidazole **199** (Example 10) according to *General Method 11*, to give *3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid* **199**, after recrystallization, as a pale yellow solid (0.05 g, 71.4%).

Data for *3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid* **199**: ^{1}H-NMR (400 MHz, $CDCl_3$ + 5% CD_3OD): 8.09 (d, 2H, J = 7.6), 7.67-7.56 (m, 3H), 7.51 (d, 2H, J = 7.6), 7.44 (d, 2H, J = 7.6), 7.42-7.34 (m, 5H), 6.45 (d, 2H, J = 16.0), 5.18-5.05 (m, 1H), 4.30-4.15 (m, 2H), 3.62-3.40 (m, 2H), 3.38-3.15 (m, 2H), 1.78-1.45 (m, 2H), 1.35-1.10 (m, 21H), 0.81 (t, 3H, J = 6.6); MS (APcI): 745.6 (100, [M+H]); calcd $C_{45}H_{53}N_4O_6$ ([M+H]) 745.9.

Example 11

3-(4-{2-(2,4-Dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid 200



200

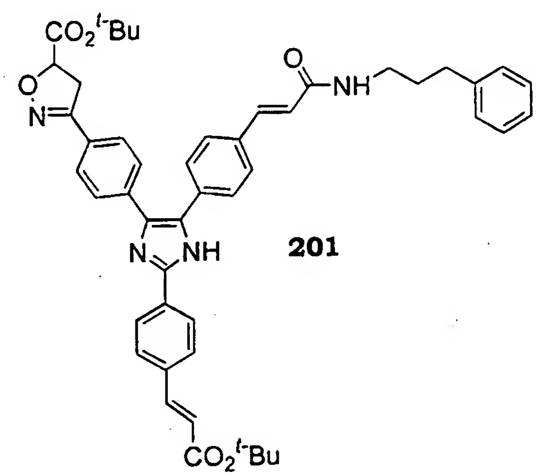
Compound **200** was synthesized according to *General Method 7* from dione ***46b*** (0.3 g, 0.49 mmol) in acetic acid (4 mL), 5-formyluracil (0.072 g, 0.51 mmol) and NH_4OAc (1.13 g, 14.61 mmol), which gives 3-(4-{2-(2,4-Dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester. The *tert*-butyl ester was hydrolyzed according to *General Method 11* to give, after recrystallization *3-(4-{2-(2,4-Dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid* **200** as a yellow solid (0.07 g, 21%).

Data for *3-(4-{2-(2,4-Dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid* **200**: ^{1}H-NMR (300 MHz, DMSO-d_6): 12.09 (br s, 1H), 12.05 (s, 1H), 8.49 (d, 2H, *J* = 6.0), 8.30 (t, 1H, *J* = 5.6), 7.95 (d, 2H, *J* = 8.4), 7.81 (d, 2H, *J* = 8.4), 7.75 (d, 2H, *J* = 8.4), 7.69 (d, 2H, *J* = 8.1), 7.60 (d,

1H, J = 16.2), 6.84 (d, 2H, J = 15.9), 5.38 (dd, 1H, J = 11.7, 6.6), 3.93 (dd, 1H, J = 17.1, 11.4), 3.78 (dd, 1H, J = 17.4, 6.6), 3.40-3.30 (m, 2H), 1.70-1.55 (m, 2H), 1.42 (br s, 18H), 1.02 (t, 3H, J = 6.6); MS (APcI): 681.2 (100, [M+H]); calcd $C_{38}H_{45}N_6O_6$ ([M+H]) 681.8.

Example 12

3-[4-(2-[4-((E)-2-*tert*-Butoxycarbonyl-vinyl)-phenyl]-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 201



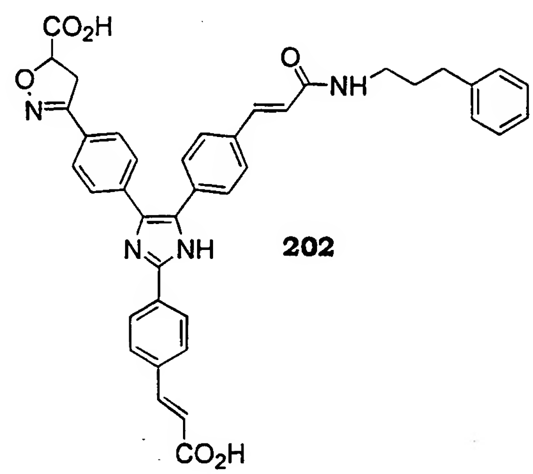
201

Compound **201** was synthesized according to *General Method 7* from dione **46i** ($R^{1'}$ = *tert*-butyl ester, $R^{2'}$ = $-(CH_2)_3Ph$) (0.73 g, 1.29 mmol) in acetic acid (6 mL), 4-formylcinnamic acid *tert*-butyl ester (0.36 g, 1.55 mmol) and NH_4OAc (3.0 g, 38.7 mmol). The resulting imidazole was purified by flash column chromatography eluting with DCM/MeOH (95:5). The desired imidazole *3-[4-(2-[4-((E)-2-tert-Butoxycarbonyl-vinyl)-phenyl]-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **201** was obtained as a yellow solid (0.42 g, 42%).

Data for *3-[4-(2-[4-((E)-2-tert-Butoxycarbonyl-vinyl)-phenyl]-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **201**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.15 (br s, 2H), 7.65-7.40 (br m, 12H), 7.30-7.10 (br m, 5H), 6.40-6.20 (br m, 3H), 5.04 (t, 1H, J = 7.5), 3.55 (d, 2H, J = 7.5), 3.34 (br s, 2H), 2.58 (br s, 2H), 1.84 (br s, 2H), 1.58 (s, 9H), 1.53 (s, 9H).

Example 13

3-[4-(2-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid 202



202

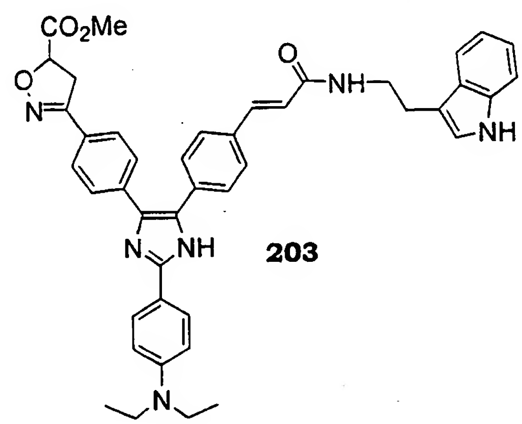
The bis-*tert*-butyl ester of imidazole **202** was hydrolyzed according to *General Method 11* to give, after recrystallization, the desired imidazole *3-[4-(2-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid* **202** as a yellow solid (0.13 g, 36%).

Data for *3-[4-(2-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenyl]-4,5-dihydro-*

isoxazole-5-carboxylic acid **202**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.20-8.14 (m, 3H), 7.86 (d, 2H, J=7.8), 7.88 (d, 2H, J= 8.1), 7.69-7.57 (m, 7H), 7.45 (d, 1H, J=15.6), 7.32-7.18 (m, 5H), 6.67 (d, 1H, J=15.9), 6.63 (d, 1H, J=15.9), 5.22-5.16 (m, 1H), 3.81-3.51 (m, 2H), 3.23-3.17 (m, 2H), 2.65-2.60 (m, 2H), 1.82-1.72 (m, 2H).

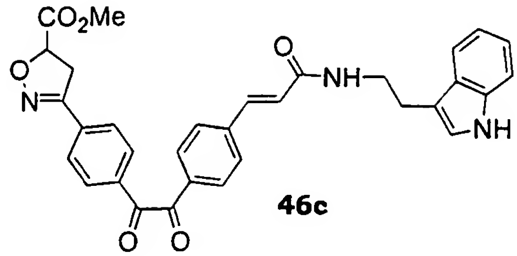
Example 14

3-{4-[2-(4-Diethylamino-phenyl)-5-(4-{(E)-2-[2-(1*H*-indol-3-yl)-ethylcarbamoyl]-vinyl}-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester 203



203

Dione **46c** (Scheme 9) was synthesized according to *General Method 6* from dione **44b** (see Example 1 for synthesis of **44b**)(0.1 g, 0.25 mmol) in $CHCl_3$ (2 mL), EDCI (0.052 g, 0.27 mmol), HOBt (0.037, 0.27 mmol), DIEA (0.063g, 0.5 mmol), and tryptamine **26c** (0.043g, 0.27 mmol). After purification *via* column chromatography eluting with ethyl acetate:hexane the desired dione 3-{4-[2-(4-{(E)-2-[2-(1H-Indol-3-yl)-ethylcarbamoyl]-vinyl}-phenyl)-2-oxo-ethanoyl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester **46c** was obtained (0.08 g, 53.9%).



46c

Data for *3-{4-[2-(4-{(E)-2-[2-(1H-Indol-3-yl)-ethylcarbamoyl]-vinyl}-phenyl)-2-oxo-ethanoyl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester* **46c**: ^{1}H-NMR (400 MHz, $CDCl_3$): 8.31 (s, 1H), 7.99 (d, 2H, J = 8.4), 7.92 (d, 2H, J = 8.0), 7.79 (d, 2H, J = 8.8), 7.68-7.47 (m, 4H), 7.36 (d, 1H, J = 8.0), 7.19 (t, 1H, J = 7.4), 7.10 (t, 1H, J = 7.4), 7.04 (s, 1H), 6.41 (d, 1H, J = 16.4), 5.96 (br t, 1H, J = 5.6), 5.23 (dd, 1H, J = 10.8, 7.2), 3.82 (s, 3H), 3.80-3.55 (m, 4H), 3.03 (t, 2H, J = 6.6).

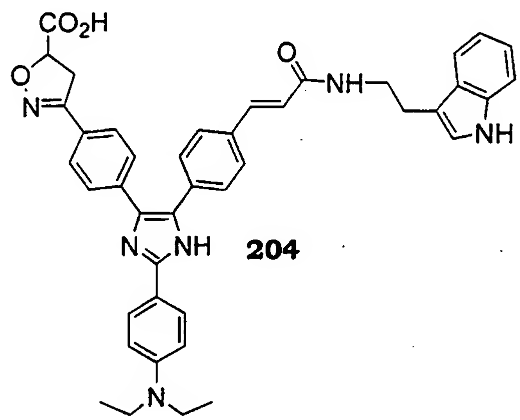
Compound **203** was synthesized according to *General Method 7* from dione **46c** (0.066 g, 0.12 mmol) in acetic acid (1.5 mL) 4-diethylamino-benzaldehyde (0.024 g, 0.13 mmol) and NH_4OAc (0.28 g, 3.6 mmol). Purification by column chromatography eluting with hexane/EtOAc gave *3-{4-[2-(4-Diethylamino-phenyl)-5-(4-{(E)-2-[2-(1H-indol-3-yl)-ethylcarbamoyl]-vinyl}-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester* **203** (0.03 , 35.4%).

Data for *3-{4-[2-(4-Diethylamino-phenyl)-5-(4-{(E)-2-[2-(1H-indol-3-yl)-ethylcarbamoyl]-vinyl}-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester* **203**: ^{1}H-NMR (300 MHz, $CDCl_3$): 7.80 (d, 2H, J = 8.8), 7.60-7.24 (m, 11H), 7.14 (t, 1H, J = 7.6), 7.06 (t, 1H, J = 7.4), 7.02 (s, 1H), 6.67 (br s, 2H), 6.47 (t, 1H, J = 5.0), 6.24 (d, 1H, J = 15.2),

5.12 (t, 1H, J = 9.2), 3.78 (s, 3H), 3.65 (t, 2H, J = 6.2), 3.56 (d, 2H, J = 6.6), 3.53 (br s, 4H), 2.99 (t, 2H, J = 6.6), 1.41 (t, 6H, J = 7.0); MS (ESI): 707.6 (100, [M+H]); calcd $C_{43}H_{42}N_5O_4$ ([M+H]) 707.8.

Example 15

3-{4-[2-(4-Diethylamino-phenyl)-5-(4-{(E)-2-[2-(1*H*-indol-3-yl)-ethylcarbamoyl]-vinyl}-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid 204



204

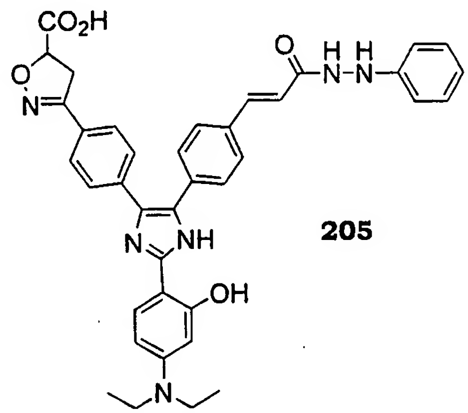
Imidazole **204** was synthesized according to *General Method 10* from imidazole **203** (0.03 g, 0.04 mmol), 1N LiOH (0.06 mL), and 1,4-Dioxane (0.6 mL). *3-{4-[2-(4-Diethylamino-phenyl)-5-(4-{(E)-2-[2-(1H-indol-3-yl)-ethylcarbamoyl]-vinyl}-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid* **204** was obtained, after recrystallization, as a pale yellow solid (0.02 g, 66.7%).

Data for *3-{4-[2-(4-Diethylamino-phenyl)-5-(4-{(E)-2-[2-(1H-indol-3-yl)-ethylcarbamoyl]-vinyl}-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid* **204**: : ^{1}H-NMR (300 MHz, $CDCl_3$): 8.09 (br s, 2H), 7.90-7.82 (m, 2H), 7.78-7.70 (m, 2H), 7.68-7.45 (m, 7H), 7.35-7.25 (m, 1H),

7.10-7.02 (m, 1H), 7.02-6.94 (m, 1H), 6.89-6.80 (m, 2H), 6.66-6.55 (m, 1H), 5.20-5.10 (m, 1H), 3.80-3.40 (m, 8H), 3.05-2.95 (m, 2H), 1.31-1.10 (m, 6H).

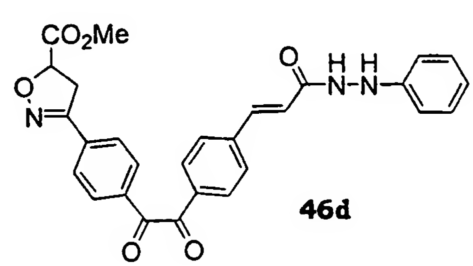
Example 16

3-[4-(2-(4-Diethylamino-2-hydroxy-phenyl)-5-{4-[(E)-2-(*N*-phenyl-hydrazinocarbonyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid 205



205

Dione **46d** (Scheme 9) was synthesized according to *General Method 6* from dione **44b** (see Example 1 for synthesis of **44b**)(0.1 g, 0.22 mmol) in $CHCl_3$ (1.5 mL), EDCI (0.064 g, 0.33 mmol), HOBt (0.045 g, 0.33 mmol), DIEA (0.11 g, 0.89 mmol), and phenylhydrazine **26d** (0.04 g, 0.33 mmol). After purification *via* column chromatography eluting with ethyl acetate:hexane the desired dione *3-[4-(2-Oxo-2-{4-[(E)-2-(N'-phenyl-hydrazinocarbonyl)-vinyl]-phenyl}-ethanoyl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester* **46d** was obtained (0.11 g, 92.7%).



46d

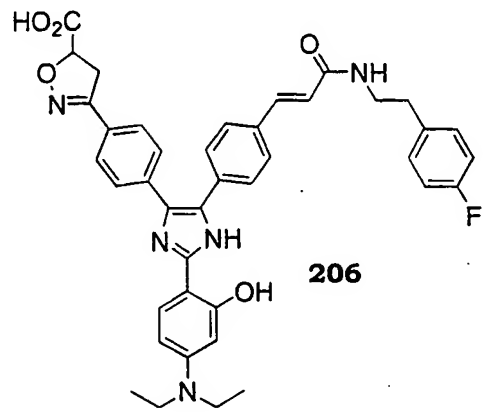
Data for *3-[4-(2-Oxo-2-{4-[(E)-2-(N'-phenyl-hydrazinocarbonyl)-vinyl]-phenyl}-ethanoyl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester* **46d**: ^{1}H-NMR (300 MHz, $CDCl_3$): 8.76 (brs, 1H), 7.97 (d, 2H, *J* = 8.4), 7.89 (d, 2H, *J* = 8.4), 7.77 (d, 2H, *J* = 8.4), 7.58-7.52 (m, 2H), 7.24-7.13 (m, 3H), 6.89-6.77 (m, 3H), 6.71 (d, 1H, *J* = 15.6), 6.48 (brs, 1H), 5.10 (t, 1H, *J* = 9.6), 3.57 (d, 2H, *J* = 9.3), 1.50 (s, 9H).

Compound **205** was synthesized according to *General Method 7* from dione **46d** (0.11 g, 0.2 mmol) in acetic acid (2 mL), 2-hydroxy-4-diethylamino-benzaldehyde (0.06 g, 0.3 mmol) and NH_4OAc (0.47 g, 6 mmol), which gives 3-[4-(2-(4-Diethylamino-2-hydroxy-phenyl)-5-{4-[(E)-2-(*N*-phenyl-hydrazinocarbonyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester. The methyl ester was hydrolyzed according to *General Method 10* to give, after recrystallization, the desired imidazole *3-[4-(2-(4-Diethylamino-2-hydroxy-phenyl)-5-{4-[(E)-2-(N-phenyl-hydrazinocarbonyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid* **205** as a yellow solid (0.02 g, 15.2%).

Data for *3-[4-(2-(4-Diethylamino-2-hydroxy-phenyl)-5-{4-[(E)-2-(N-phenyl-hydrazinocarbonyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid* **205**: ^{1}H-NMR (400 MHz, DMSO-d_6): 9.95 (s, 1H), 7.77-7.51 (m, 11H), 7.13 (t, 2H, *J* = 7.6), 6.78-6.68 (m, 3H), 6.32 (br d, 1H, *J* = 6.8), 6.18 (br s, 1H), 7.74 (s, 1H), 5.18 (dd, 1H, *J* = 10.8, 6.4), 3.77-3.55 (d, 2H), 3.33 (br s, 4H), 1.11 (t, 6H, *J* = 7.0). MS (ESI): 657.6 (20, [M+H]), 579.6 (15), 301.5 (100); calcd $C_{38}H_{37}N_6O_5$ ([M+H]) 657.3.

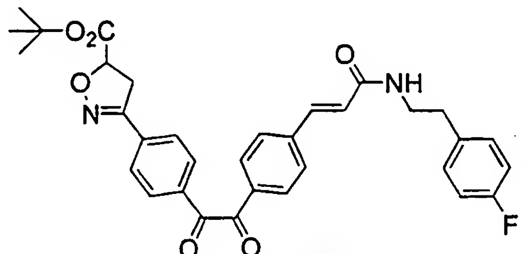
Example 17

3-{4-[2-(4-Diethylamino-2-hydroxy-phenyl)-5-(4-{(E)-2-[2-(4-fluoro-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid 206



206

Dione **46e** (Scheme 9) was synthesized according to *General Method 6* from dione **44b** (for synthesis of **44b** see Example 7)(1 g, 2.2 mmol) in $CHCl_3$ (15 mL), EDCI (0.64 g, 3.3 mmol), HOBt (0.45 g, 3.3 mmol), DIEA (0.72 g. 5.6 mmol), and 4-fluorophenethylamine **26e** (0.46 mL, 3.3 mmol). After purification *via* column chromatography eluting with ethyl acetate:hexane the desired dione *3-{4-[2-(4-{(E)-2-[2-(4-Fluoro-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-2-oxo-ethanoyl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **46e** was obtained (1.1 g, 87.7%).



46e

Data for *3-{4-[2-(4-{(E)-2-[2-(4-Fluoro-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-2-oxo-ethanoyl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **46e**: ^{1}H-NMR (300 MHz, $CDCl_3$): 8.02 (d, 2H, J = 8.4), 7.97 (d, 2H, J = 8.4), 7.82 (d, 2H, J = 8.4), 7.68 (d, 1H, J = 15.6), 7.62 (d, 2H, J = 8.4), 7.21-7.16

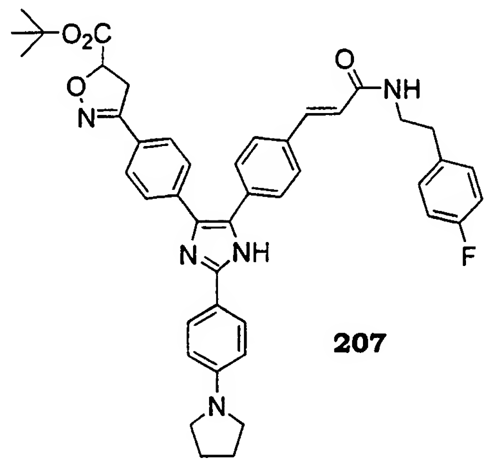
(m, 2H), 7.05-6.99 (m, 2H), 6.45 (d, 1H, J = 15.6), 5.70 (t, 1H, J = 6.0), 5.15-5.09 (m, 1H), 3.69-3.58 (m, 4H), 2.88 (t, 2H, J = 6.9), 1.51 (s, 9H).

Compound **206** was synthesized according to *General Method 7* from dione **46e** (0.11 g, 0.21 mmol) in acetic acid (2 mL), 2-hydroxy-4-diethylamino-benzaldehyde (0.06 g, 0.32 mmol) and NH_4OAc (0.49 g, 6.4 mmol), which gives 3-{4-[2-(4-Diethylamino-2-hydroxy-phenyl)-5-(4-{(E)-2-[2-(4-fluoro-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester. The *tert*-butyl ester was hydrolyzed according to *General Method 11* to give, after recrystallization 3-{4-[2-(4-Diethylamino-2-hydroxy-phenyl)-5-(4-{(E)-2-[2-(4-fluoro-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid **206** as a yellow solid (0.08 g, 55%).

Data for *3-{4-[2-(4-Diethylamino-2-hydroxy-phenyl)-5-(4-{(E)-2-[2-(4-fluoro-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid* **206**: ^{1}H-NMR (400 MHz, $CDCl_3/CD_3OD$): 8.33 (s, 1H), 7.43-7.38 (m, 4H), 7.35 (d, 2H, J = 5.2), 7.32 (d, 2H, J = 6.4), 7.27 (d, 2H, J = 6.4), 7.00-6.97 (m, 2H), 6.77 (t, 2H, J = 8.4), 6.28 (d, 1H, J = 16), 6.09 (d, 1H, J = 9.6), 6.08 (s, 1H), 4.83-4.78 (m, 1H), 3.48-3.35 (m, 2H), 3.32 (t, 2H, J = 7.6), 3.18 (dd, 4H, J = 14.0, 7.2), 2.64 (t, 2H, J = 7.6), 0.98 (t, 6H, J = 6.8). MS (ESI): 688.6 (50, [M+H]), 333.5 (100); calcd $C_{40}H_{39}FN_5O_5$ ([M+H]) 688.3.

Example 18

3-{4-[5-(4-{(E)-2-[2-(4-Fluoro-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-2-(4-pyrrolidin-1-yl-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 207



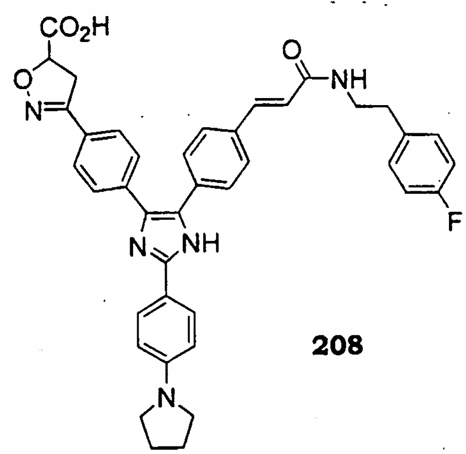
207

Compound **207** was synthesized according to *General Method 7* from dione **46e** (0.5 g, 0.88 mmol) in acetic acid (7 mL), 4-pyrrolidin-1-yl-benzaldehyde (0.17 g, 0.96 mmol) and NH_4OAc (2 g, 26.3 mmol). The resulting imidazole was purified by flash column chromatography eluting with hexane/ethyl acetate (3:1). The desired imidazole *3-{4-[5-(4-{(E)-2-[2-(4-Fluoro-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-2-(4-pyrrolidin-1-yl-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **207** was obtained as a yellow solid (0.21 g, 32.8%).

Data for *3-{4-[5-(4-{(E)-2-[2-(4-Fluoro-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-2-(4-pyrrolidin-1-yl-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **207**: ^{1}H-NMR (300 MHz, DMSO): 7.92 (br s, 2H), 7.69-7.53 (br m, 5H), 7.40-7.20 (br m, 4H), 7.07 (br s, 2H), 7.00-6.88 (br m, 2H), 6.56 (d, 2H, J = 8.7), 6.40-6.14 (br m, 2H), 5.03 (t, 1H, J = 9.15), 3.58 (br s, 2H), 3.54 (d, 2H, J = 9.3), 3.30 (br s, 4H), 2.80 (br s, 2H), 1.02 (t, 4H, J = 6.5).

Example 19

3-{4-[5-(4-{(E)-2-[2-(4-Fluoro-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-2-(4-pyrrolidin-1-yl-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid 208



208

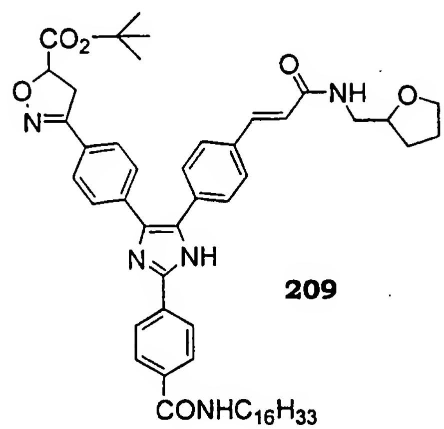
Imidazole **208** was synthesized according to *General Method 11 via* hydrolyses of the *tert*-butyl ester of imidazole **207** according to *General Method 11*, to give *3-{4-[5-(4-{(E)-2-[2-(4-Fluoro-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-2-(4-pyrrolidin-1-yl-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid* **208**, after recrystallization as a pale yellow solid (0.19 g, 90%).

Data for *3-{4-[5-(4-{(E)-2-[2-(4-Fluoro-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-2-(4-pyrrolidin-1-yl-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid* **208**: ^{1}H-NMR (300 MHz, DMSO): 8.20 (t, 1H, J = 5.5), 7.96 (d, 2H, J = 9.0), 7.76 (d, 2H, J = 8.7), 7.63 (d, 2H, J = 8.4), 7.61 (d, 2H, J = 8.4), 7.55 (d, 2H, J = 8.7), 7.44 (d, 1H, J = 15.9), 7.29 (d, 1H, J = 8.7), 7.26 (d, 1H, J = 8.7), 7.13 (d, 1H, J = 9.0), 7.10 (d, 1H, J = 9.0), 6.70 (d, 2H, J = 9.3), 6.64 (d, 1H, J = 15.9), 5.20 (dd, 1H, J = 11.7, J = 6.6), 3.80-3.56 (m, 2H), 3.34 (br

s, 6H), 2.78 (t, 2H, J = 7.1), 1.99 (t, 4H, J = 7.5). MS (ESI): 670.7 (100, [M+H]); calcd $C_{40}H_{37}FN_5O_4$ [M+H] 670.3.

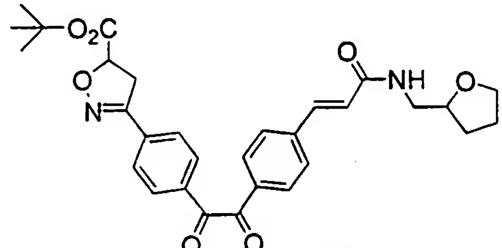
Example 20

3-{4-[2-(4-Hexadecylcarbamoyl-phenyl)-5-(4-{(E)-2-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-vinyl}-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 209



209

Dione **46f** (Scheme 9) was synthesized according to *General Method 6* from dione **44a** (for synthesis of **44a** see Example 7) (300 mg, 0.67 mmol) in CH_2Cl_2 (1.5 mL), EDCI (141 mg, 0.73 mmol), HOBt (99 mg, 0.73 mmol), DIEA (234 μL, 1.34 mmol), and tetrahydrofurfurylamine **26f** (75.8 μL, 0.73 mmol). After purification *via* column chromatography eluting with ethyl acetate:hexane the desired dione *3-{4-[2-Oxo-2-(4-{(E)-2-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-vinyl}-phenyl)-ethanoyl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **46f** was obtained (150 mg, 41%).



46f

Data for *3-{4-[2-Oxo-2-(4-{(E)-2-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-vinyl}-phenyl)-ethanoyl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid tert-*

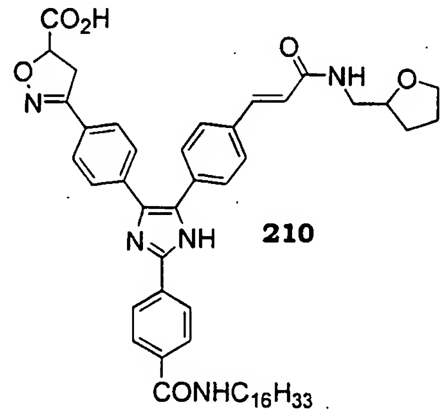
butyl ester **46f**: ^{1}H-NMR (300 MHz, $CDCl_3$): 8.03 (d, 2H, J = 8.4), 7.98 (d, 2H, J = 8.4), 7.83 (d, 2H, J = 8.4), 7.69-7.62 (m, 3H), 6.56 (d, 1H, J = 15.6), 6.21 (t, 1H, J = 7.2), 5.12 (dd, 1H, J = 10.2, 9.0), 4.07-4.03 (m, 1H), 3.93-3.83 (m, 1H), 3.90-3.72 (m, 2H), 3.61 (d, 2H, J = 9.9), 3.31-3.22 (m, 1H), 2.26-2.89 (m, 4H), 1.52 (s, 9H).

Compound **209** was synthesized according to *General Method 7* from dione **46f** (150 mg, 0.27 mmol) in acetic acid (2 mL), with 4-Formyl-*N*-hexadecyl-benzamide (154 mg, 0.41 mmol) and NH_4OAc (634 mg, 8.22 mmol). The resulting imidazole was purified by flash column chromatography eluting with 0.5-5% methanol dichloromethane. The desired imidazole *3-{4-[2-(4-Hexadecylcarbamoyl-phenyl)-5-(4-{(E)-2-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-vinyl}-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **209** was obtained as a yellow solid (200 mg, 82%).

Data for *3-{4-[2-(4-Hexadecylcarbamoyl-phenyl)-5-(4-{(E)-2-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-vinyl}-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **209**: ^{1}H-NMR (400 MHz, $CDCl_3$): 8.05 (brs, 2H), 7.68 (d, 2H, J = 6.8), 7.49 (brs, 4H), 7.36 (brs, 3H), 7.21 (brs, 2H), 6.71 (brs, 1H), 6.56 (brs, 1H), 6.30 (d, 1H, J = 16.0), 5.02 (dd, 1H, J = 10.0, 8.0), 3.98 (brs, 1H), 3.85 (q, 1H, J = 7.2), 3.74 (q, 1H, J = 6.8), 3.70-3.61 (m, 1H), 3.53-3.49 (m, 2H), 3.38-3.37 (m, 2H), 3.23-3.21 (m 1H), 1.91-1.86 (m, 4H), 1.58-1.44 (m, 11H), 1.23 (brs, 26H), 0.86 (t, 3H, J = 6.8).

Example 21

3-{4-[2-(4-Hexadecylcarbamoyl-phenyl)-5-(4-{(E)-2-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-vinyl}-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid 210



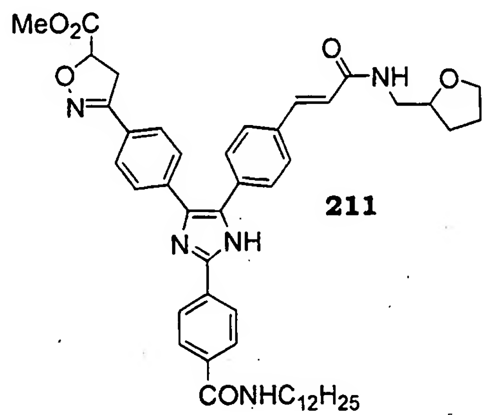
210

Imidazole **210** was synthesized according to *General Method 11 via* hydrolyses of the *tert*-butyl ester of imidazole **209**. After purification the desired imidazole *3-{4-[2-(4-Hexadecylcarbamoyl-phenyl)-5-(4-{(E)-2-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-vinyl}-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid* **210**, was obtained as a yellow solid (3.8 mg, 20%).

Data for *3-{4-[2-(4-Hexadecylcarbamoyl-phenyl)-5-(4-{(E)-2-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-vinyl}-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid* **210**: ^{1}H-NMR (300 MHz, DMSO-d$_6$): 8.68 (t, 1H, *J* = 5.1), 8.36-8.33 (m, 3H), 8.13 (d, 2H, *J* = 8.4), 7.97-7.56 (m, 9H), 6.98-6.85 (m, 1H), 5.35 (q, 1H, *J* = 6.9), 4.30-4.20 (m, 1H), 4.09-4.05 (m, 1H), 4.00-3.89 (m, 1H), 3.85-3.77 (m, 1H), 3.70-3.34 (m, 5H), 2.11-2.00 (m, 4H), 1.71-1.70 (m, 2H), 1.47-1.30 (m, 26H), 1.02 (t, 3H, *J* = 6.3).

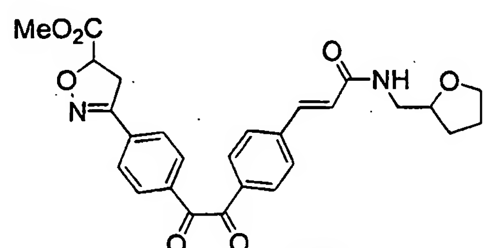
Example 22

3-{4-[2-(4-Dodecylcarbamoyl-phenyl)-5-(4-{(E)-2-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-vinyl}-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester 211



211

Dione **46g** (Scheme 9) was synthesized according to *General Method 6* from dione **44b** (see Example 1 for synthesis of **44b**) (180 mg, 0.44 mmol) in CH_2Cl_2 (3.5 mL), EDCI (127 mg, 0.66 mmol), HOBt (90 mg, 0.66 mmol), DIEA (193 μL, 1.1 mmol), and tetrahydrofurfurylamine **26f** (68 μL, 0.66 mmol). After purification *via* column chromatography eluting with ispropanol/chloroform the desired dione *3-{4-[2-Oxo-2-(4-{(E)-2-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-vinyl}-phenyl)-ethanoyl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester* **46g** was obtained (128 mg, 59%).



46g

Data for *3-{4-[2-Oxo-2-(4-{(E)-2-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-vinyl}-phenyl)-ethanoyl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester* **46g**: ^{1}H-NMR (400 MHz, $CDCl_3$): 8.01 (d, 2H, J = 8.4), 7.98 (d, 2H, J = 8.4), 7.80 (d, 2H, J = 9.2), 7.66-7.60 (m, 3H), 6.51 (d, 1H, J = 15.6), 6.08 (t, 1H, J = 7.2), 5.24 (dd, 1H, J = 10.2, 9.0), 4.04-3.98 (m, 1H), 3.90-

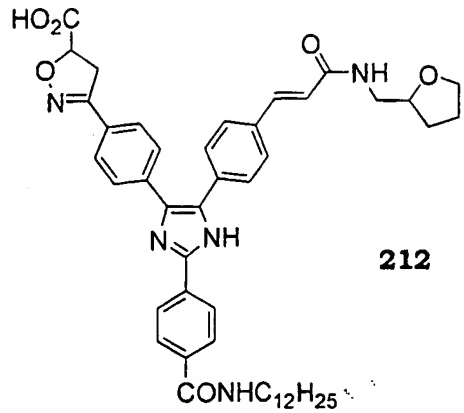
3.84 (m, 1H), 3.81 (s, 3H), 3.80-3.70 (m, 2H), 3.68-3.63 (m, 2H), 3.27-3.20 (m, 1H), 2.05-1.97 (m, 2H), 1.94-1.87 (m, 2H).

Compound **211** was synthesized according to *General Method 7* from dione **46g** (247 mg, 0.5 mmol) in acetic acid (1 mL + 250 μL DMSO), with 4-Formyl-*N*-dodecyl-benzamide (240 mg, 0.76 mmol) and NH_4OAc (1.2 g, 15.1 mmol). The resulting imidazole was purified by flash column chromatography eluting with methanol/dichloromethane. The desired imidazole *3-{4-[2-(4-Dodecylcarbamoyl-phenyl)-5-(4-{(E)-2-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-vinyl}-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester* **211** was obtained as a yellow solid (44 mg, 11%).

Data for *3-{4-[2-(4-Dodecylcarbamoyl-phenyl)-5-(4-{(E)-2-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-vinyl}-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester* **211**: ^{1}H-NMR (300 MHz, $CDCl_3$): 8.06 (d, 2H, J = 7.2), 7.69 (d, 2H, J = 6.8), 7.52 (brs, 5H), 7.41-7.39 (m, 2H), 7.28-7.22 (m, 2H), 6.52 (brs, 1H), 6.40 (brs, 1H), 6.29 (d, 1H, J = 15.6), 5.15 (t, 1H, J = 9.0), 3.98 (brs, 1H), 3.85-3.72 (m, 4H), 3.66-3.54 (m, 3H), 3.40-3.37 (m, 2H), 3.25-3.16 (m, 1H), 1.98-1.83 (m, 4H), 1.67-1.44 (m, 5H), 1.22 (brs, 18H), 0.83 (t, 6H, J = 5.6).

Example 23

3-{4-[2-(4-Dodecylcarbamoyl-phenyl)-5-(4-{(E)-2-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-vinyl}-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid 212



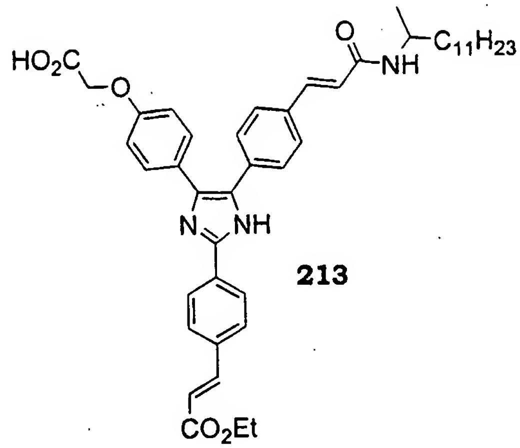
212

Imidazole **212** was synthesized according to *General Method 10 via* hydrolyses of the methyl ester of imidazole **211,** to give *3-{4-[2-(4-Dodecylcarbamoyl-phenyl)-5-(4-{(E)-2-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-vinyl}-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid* **212**, after purification, as a white solid (12 mg, 31%).

Data for *3-{4-[2-(4-Dodecylcarbamoyl-phenyl)-5-(4-{(E)-2-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-vinyl}-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid* **212**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.49 (t, 1H, J = 5.4), 8.17 (d, 3H, J = 8.1), 7.91 (d, 2H, J = 8.1), 7.65-7.53 (m, 8H), 7.41 (d, 1H, J = 15.6), 6.71 (d, 1H, J = 15.6), 4.65 (t, 1H, J = 9.0), 3.90-3.84 (m, 1H), 3.77 (dd, 1H, J = 14.4, 8.1), 3.62 (dd, 1H, J = 14.7, 7.5), 3.42-3.22 (m, 6H), 1.88-1.77 (m, 4H), 1.59-1.49 (m, 2H), 1.23 (s, 18H), 0.84 (t, 3H, J = 5.6).

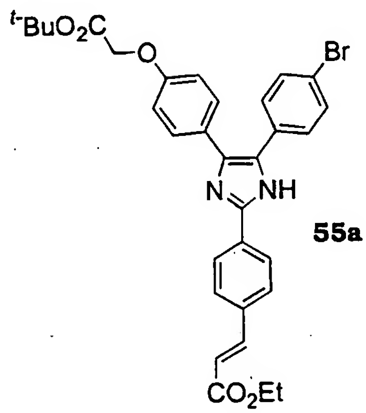
Example 24

[4-(2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-{4-[(E)-2-(1-methyl-dodecylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenoxy]-acetic acid 213



213

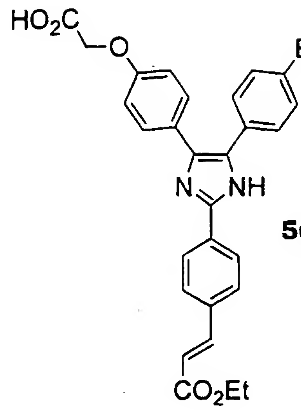
Imidazole **56** was synthesized according to *General Method 7* from dione **54** (4.6 g, 11 mmol) in acetic acid (11 mL), with 4-formylcinnamic acid ethyl ester (3.4 g, 16.5 mmol) and NH_4OAc (25.4 g, 330 mmol), which gives imidazole **55a** (5 g, 75%) (dione **54** was synthesized according to *General Method 4*).



55a

Data for **55a** (R[1]' = *tert*-butyl): ^{1}H-NMR (300 MHz, $CDCl_3$): 7.92 (d, 2H, J = 7.5), 7.64 (d, 1H, J = 15.9), 7.53 (d, 2H, J = 8.1), 7.43-7.32 (m, 6H), 6.82 (d, 2H, J = 8.1), 6.43 (d, 1H, J = 15.9), 4.51 (s, 2H), 4.24 (q, 2H, J = 6.9), 1.48 (s, 9H), 1.31 (t, 3H, J = 7.2).

The *tert*-butyl ester of **55a** (4.2 g, 6.9 mmol)(Scheme 11) was hydrolyzed according to *General Method 11* to give after recrystallization, imidazole **56a** (3.2 g, 84%).



56a

Data for **56a**: ^{1}H-NMR (300 MHz, $CDCl_3$): 8.12 (d, 2H, J = 8.4), 7.93 (d, 2H, J = 8.7), 7.63 (d, 1H, J = 15.9), 7.63 (d, 2H, J = 8.4), 7.49 (d, 2H, J = 9.0), 7.44 (d, 2H, J = 9.0), 7.02 (d, 2H, J = 8.7), 6.77 (d, 1H, J = 16.2), 4.74 (s, 2H), 4.20 (q, 2H, J = 6.9), 1.26 (t, 3H, J = 7.2).

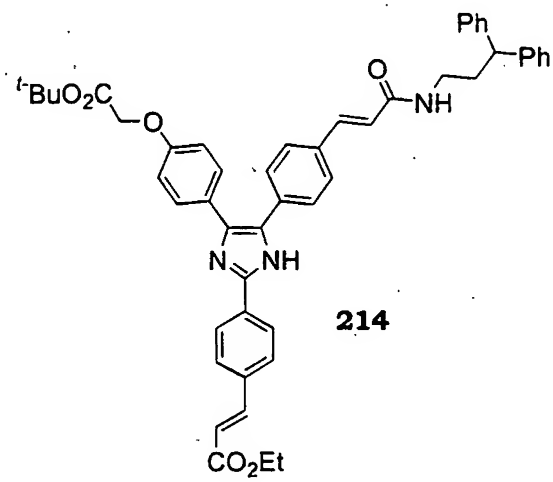
Compound **213** was synthesized according to *General Method 8* from imidazole **56a** (400 mg, 0.73 mmol) in DMF (5 mL), with $Pd(OAc)_2$ (33 mg, 0.15 mmol), TEA (302 μL, 1.46 mmol), (*o*-Tolyl)$_3$P (89 mg, 0.29 mmol), and *acrylamide **57a** (222 mg, 0.88 mmol) to give after purification by flash column chromatography and recrystallization *[4-(2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-{4-[(E)-2-(1-methyl-dodecylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenoxy]-acetic acid* **213** as a yellow solid (30 mg, 38%). *Acrylamide **57a** was synthesized according to *General Method 9* from acryloyl chloride and 1-methyl dodecylamine.

Data for *[4-(2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-{4-[(E)-2-(1-methyl-dodecylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenoxy]-acetic acid* **213**: ^{1}H-NMR (400 MHz, DMSO-d_6): 8.12 (d, 2H, J = 7.7), 7.92-7.87 (m, 3H), 7.68 (d, 1H, J = 16.0), 7.59-7.53 (m, 4H), 7.45 (d, 2H, J = 8.0), 7.38 (d, 1H, J = 16.0), 7.00 (d, 2H, J = 8.4), 6.72 (d, 1H, J = 16.0), 6.60 (d, 1H, J = 16.0), 4.73

(s, 2H), 4.20 (q, 2H, J = 7.2), 3.85 (m, 1H, J = 6.4), 1.39 (brs, 2H), 1.28- 1.22 (m, 21H), 1.06 (d, 3H, J = 6.4), 0.83 (t, 3H, J = 6.4). LC/MS: LC: retention time 3.78 minutes; MS (APcI): 720.5 (100, [M+H]); calcd $C_{44}H_{53}N_3O_6$ [M+H] 720.9.

Example 25

(4-{5-{4-[(E)-2-(3,3-Diphenyl-propylcarbamoyl)-vinyl]-phenyl}-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenoxy)-acetic acid *tert*-butyl ester 214



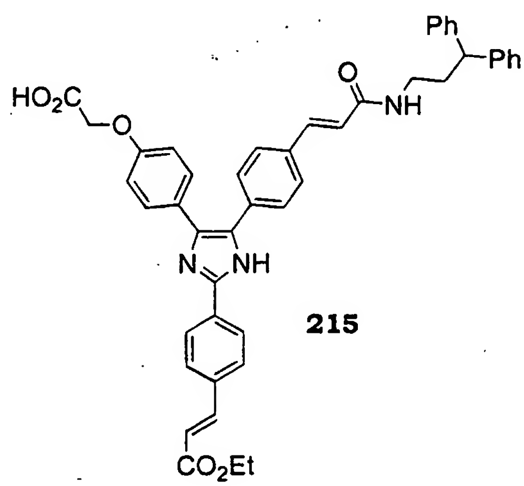
214

Compound **214** was synthesized according to *General Method 8* from imidazole **55a** (200 mg, 0.33 mmol) in DMF (2 mL), with $Pd(OAc)_2$ (15 mg, 0.07 mmol), TEA (70 μL, 0.5 mmol), (o-Tolyl)$_3$P (40 mg, 0.13 mmol), and *acrylamide **57b** (0.88 mmol) to give after recrystallization *(4-{5-{4-[(E)-2-(3,3-Diphenyl-propylcarbamoyl)-vinyl]-phenyl}-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenoxy)-acetic acid tert-butyl ester* **214** as a yellow solid 130mg, (50%). *Acrylamide **57b** was synthesized according to *General Method 9* from acryloyl chloride and 3,3-Diphenyl-propylamine.

Data for *(4-{5-{4-[(E)-2-(3,3-Diphenyl-propylcarbamoyl)-vinyl]-phenyl}-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenoxy)-acetic acid tert-butyl ester* **214**: ^{1}H-NMR (300 MHz, $CDCl_3$): 8.04 (d, 2H, J = 7.5), 7.60 (d, 1H, J = 15.9), 7.45-7.31 (m, 7H), 7.21-7.10 (m, 12H), 6.66 (d, 2H, J = 8.7), 6.36 (d, 1H, J = 15.9), 6.22 (brs, 1H), 6.13 (d, 1H, J = 15.3), 4.44 (s, 2H), 4.24 (q, 2H, J = 6.9), 3.86 (t, 1H, J = 6.9), 3.22 (q, 2H, J = 6.0), 2.22 (q, 2H, J = 6.9), 1.46 (s, 9H), 1.32 (t, 3H, J = 7.2).

Example 26

(4-{5-{4-[(E)-2-(3,3-Diphenyl-propylcarbamoyl)-vinyl]-phenyl}-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenoxy)-acetic acid 215



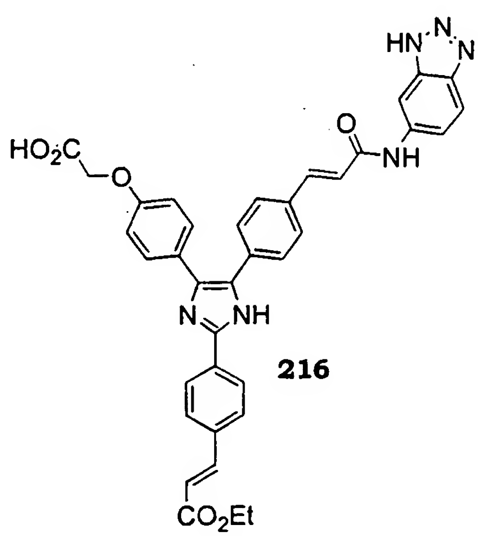
215

Imidazole **215** was synthesized according to *General Method 11 via* hydrolyses of the *tert*-butyl ester of imidazole **214** (Example 25) according to *General Method 11*, to give *(4-{5-{4-[(E)-2-(3,3-Diphenyl-propylcarbamoyl)-vinyl]-phenyl}-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenoxy)-acetic acid* **215**, after purification, as a yellow solid (50 mg, 41%).

Data for *(4-{5-{4-[(E)-2-(3,3-Diphenyl-propylcarbamoyl)-vinyl]-phenyl}-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenoxy)-acetic acid* **215**: ^{1}H-NMR (300 MHz, DMSO-d$_6$): 8.21 (t, 1H, *J* = 8.2), 8.14 (d, 2H, *J* = 8.4), 7.95 (d, 2H, *J* = 8.1), 7.70 (d, 1H, *J* = 15.9), 7.62 (d, 2H, *J* = 8.1), 7.57 (d, 2H, *J* = 8.4), 7.47 (d, 2H, *J* = 8.7), 7.41 (d, 1H, *J* = 15.9), 7.33-7.25 (m, 8H), 7.19-7.14 (m, 2H), 7.03 (d, 2H, *J* = 8.7), 6.78 (d, 1H, *J* = 15.9), 6.64 (d, 1H, *J* = 15.9), 4.75 (s, 2H), 4.20 (q, 2H, *J* = 6.6), 4.02 (t, 1H, *J* = 8.1), 3.06 (q, 2H, *J* = 5.4), 2.23 (q, 2H, *J* = 7.5), 1.26 (t, 3H, *J* = 7.2). LC/MS: LC: retention time 3.30 minute; MS (APcI): 732.7 (100, [M+H]); calcd $C_{46}H_{41}N_3O_6$ [M+H] 732.8.

Example 27

(4-{5-{4-[(E)-2-(3*H*-Benzotriazol-5-ylcarbamoyl)-vinyl]-phenyl}-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenoxy)-acetic acid 216



216

Compound **216** was synthesized according to *General Method 8* from imidazole **56** (100 mg, 0.18 mmol) in DMF (1 mL), with Pd(OAc)$_2$ (8 mg, 0.036 mmol), TEA (50.2 μL, 0.36 mmol), (*o*-Tolyl)$_3$P (22 mg, 0.072 mmol), and *acrylamide **57c** (68 mg, 0.36 mmol) to *(4-{5-{4-[(E)-2-(3H-Benzotriazol-5-*

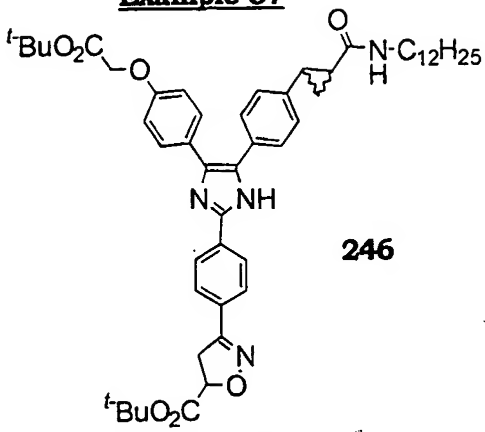
ylcarbamoyl)-vinyl]-phenyl}-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenoxy)-acetic acid **216** as a light yellow solid (5 mg, 4%). *Acrylamide **57c** was synthesized according to *General Method 9* from acryloyl chloride and 5-aminobenzotriazole.

Data *for (4-{5-{4-[(E)-2-(3H-Benzotriazol-5-ylcarbamoyl)-vinyl]-phenyl}-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenoxy)-acetic acid* **216**: ^{1}H-NMR (300 MHz, $CDCl_3$ + CD_3OD): 8.12 (d, 2H, J = 7.7), 7.65-7.55 (m, 5H), 7.42-7.28 (m, 9H), 6.85 (d, 2H, J = 7.7), 6.44 (d, 1H, J = 16.0), 4.53 (s, 2H), 4.20 (q, 2H, J = 7.2), 1.15 (d, 3H, J = 6.4). LC/MS: LC: retention time 2.53 minute; MS (APcI): 655.8 (100, [M+H]); calcd $C_{37}H_{30}N_6O_6$ [M+H] 655.7.

Example 28

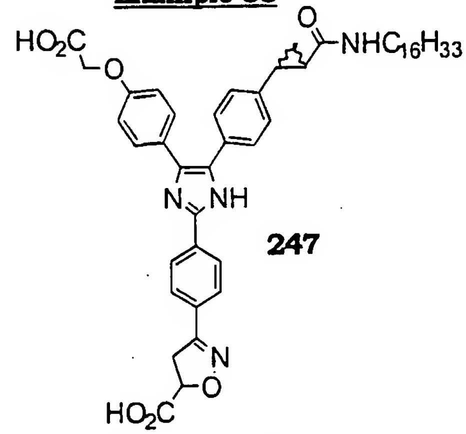
{4-[2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-(4-{(E)-2-[1-(4-pentyl-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-1*H*-imidazol-4-yl]-phenoxy}-acetic acid 217

Example 57



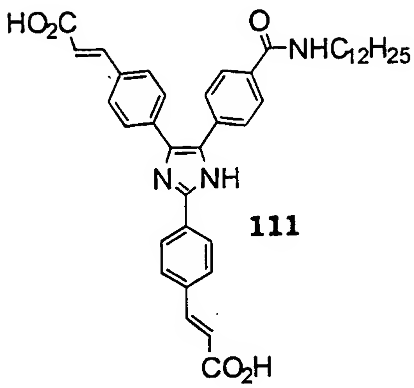
246

Example 58



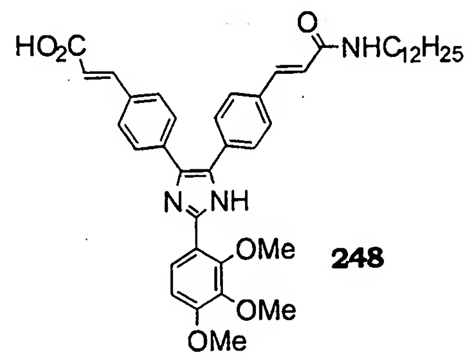
247

Example 59



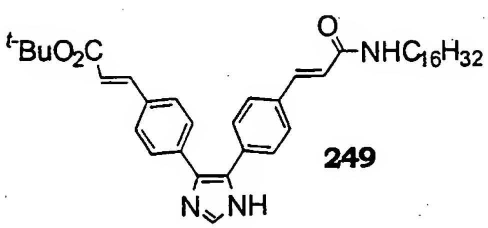
111

Example 60



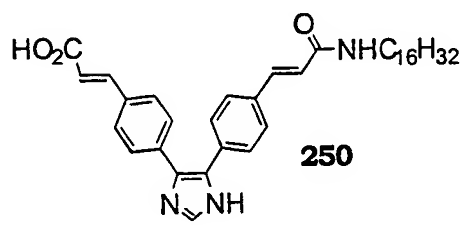
248

Example 61



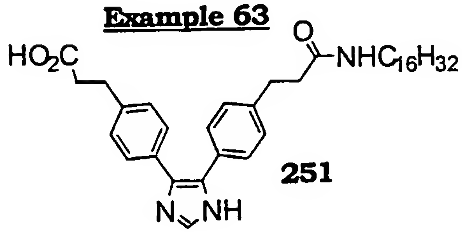
249

Example 62



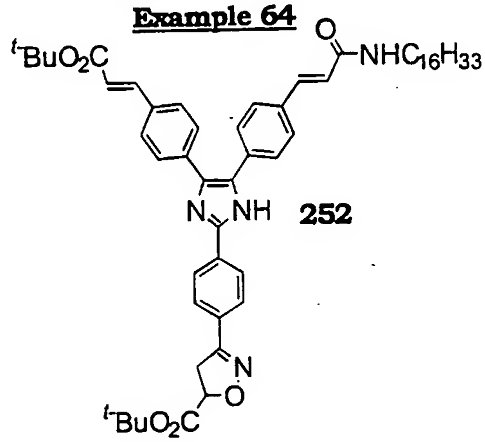
250

Example 63



251

Example 64



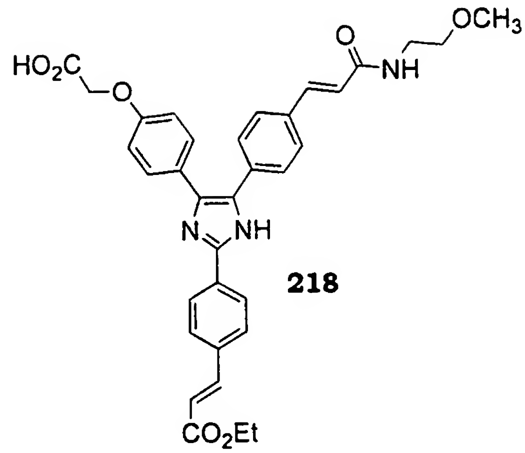
252

Compound **217** was synthesized according to *General Method 8* from imidazole **56a** (100 mg, 0.18 mmol) in DMF (1 mL), with $Pd(OAc)_2$ (8 mg, 0.036 mmol), TEA (50.2 μL, 0.36 mmol), (*o*-Tolyl)$_3$P (22 mg, 0.072 mmol), and *acrylamide **57d** (0.88 mmol) to give after purification by flash column chromatography and recrystallization *{4-[2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-(4-{(E)-2-[1-(4-pentyl-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-1H-imidazol-4-yl]-phenoxy}-acetic acid* **217** as a yellow solid (30 mg, 23%). *Acrylamide **57d** was synthesized according to *General Method 9* from acryloyl chloride and 1-(4-pentylphenyl)-ethylamine hydrochloride.

Data for *{4-[2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-(4-{(E)-2-[1-(4-pentyl-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-1H-imidazol-4-yl]-phenoxy}-acetic acid* **217**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.53 (d, 1H, J = 8.4), 8.27 (d, 2H, J = 8.4), 7.92 (d, 2H, J = 8.4), 7.69 (d, 1H, J = 15.9), 7.58 (s, 4H), 7.47 (d, 2H, J = 8.4), 7.41 (d, 1H, J = 15.9), 7.23 (d, 2H, J = 8.1), 7.12 (d, 2H, J = 8.1), 7.02 (d, 2H, J = 9.0), 6.75 (d, 1H, J = 15.6), 6.70 (d, 1H, J = 15.6), 5.01 (t, 1H, J = 6.6), 4.74 (s, 2H), 4.20 (q, 2H, J = 6.9), 2.52 (t, 2H, J = 7.5), 1.53 (m, 2H), 1.38 (d, 3H, J = 6.9), 1.29-1.23 (m, 7H), 0.84 (t, 3H, J = 6.9). LC/MS: LC: retention time 3.37 minutes; MS (APcI): 712.5 (100, [M+H]); calcd $C_{44}H_{45}N_3O_6$ [M+H] 712.8.

Example 29

[4-(2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-{4-[(E)-2-(2-methoxy-ethylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenoxy]-acetic acid 218



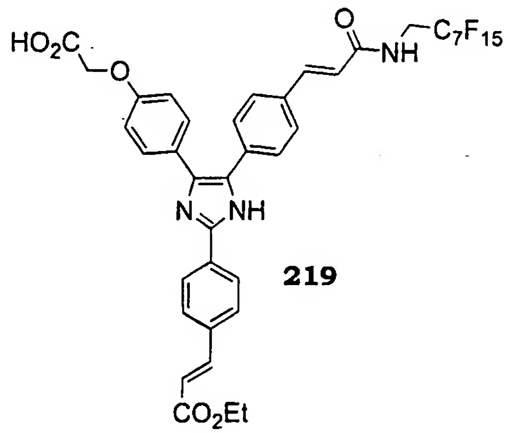
218

Compound **218** was synthesized according to *General Method 8* from imidazole **56** (400 mg, 0.73 mmol) in DMF (5 mL), with $Pd(OAc)_2$ (33 mg, 0.15 mmol), TEA (203 µL, 1.46 mmol), (*o*-Tolyl)$_3$P (89 mg, 0.29 mmol), and *acrylamide **57e** (114 mg, 0.88 mmol) to give after purification by flash column chromatography recrystallization *[4-(2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-{4-[(E)-2-(2-methoxy-ethylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenoxy]-acetic acid* **218** as a yellow solid (62 mg, 14%). *Acrylamide **57e** was synthesized according to *General Method 9* from acryloyl chloride and 2-methoxy-ethylamine.

Data for *[4-(2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-{4-[(E)-2-(2-methoxy-ethylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenoxy]-acetic acid* **218**: ^{1}H-NMR (300 MHz, DMSO-d$_6$): 8.22 (t, 1H, J = 5.1), 8.17 (d, 2H, J = 8.4), 8.01 (d, 2H, J = 8.4), 7.72 (d, 1H, J = 15.9), 7.66 (d, 2H, J = 8.4), 7.58 (d, 2H, J = 8.4), 7.50-7.42 (m, 3H), 7.06 (d, 2H, J = 9.0), 6.83 (d, 1H, J = 6.83), 6.72 (d, 1H, J = 15.9), 4.76 (s, 2H), 4.21 (q, 2H, J = 7.2), 3.41-3.26 (m, 4H), 3.26 (s, 3H), 1.27 (t, 3H, J = 7.2). LC/MS: LC: retention time 2.41 minutes; MS (APcI): 596.7 (100, [M+H]); calcd $C_{34}H_{33}N_3O_7$ [M+H] 596.6.

Example 30

[4-(2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-{4-[(E)-2-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluoro-octylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenoxy]-acetic acid 219



219

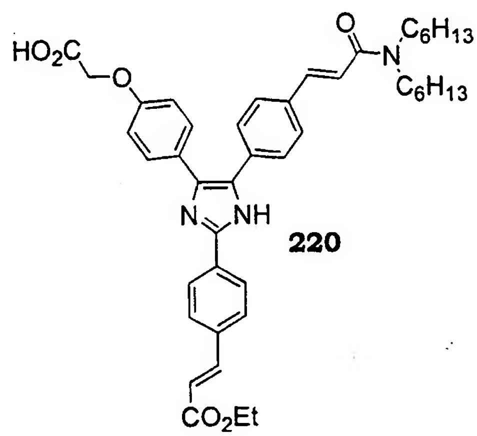
Compound **219** was synthesized according to *General Method 8* from imidazole **56** (224 mg, 0.37 mmol) in DMF (4 mL), with $Pd(OAc)_2$ (17 mg, 0.074 mmol), TEA (103 µL, 0.74 mmol), $(o\text{-Tolyl})_3P$ (45 mg, 0.15 mmol), and *acrylamide **57f** (200 mg, 0.44 mmol) to give after purification by flash column chromatograhpy and recrystallization *[4-(2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-{4-[(E)-2-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluoro-octylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenoxy]-acetic acid* **219** as a yellow solid (12 mg, 13%). *Acrylamide **57f** was synthesized according to *General Method 9* from acryloyl chloride and 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluoro-octylamine.

Data for *[4-(2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-{4-[(E)-2-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluoro-octylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenoxy]-acetic acid* **219**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.76 (t, 1H, J = 5.1), 8.13 (d, 2H, J = 8.4), 7.91 (d, 2H, J = 8.4), 7.69 (d, 1H, J = 15.9), 7.64-7.58 (m, 4H), 7.53 (d, 1H, J = 15.9), 7.46 (d, 2H, J = 8.7), 7.02 (d, 2H, J = 8.7), 6.75 (d, 1H, J = 16.2), 6.74 (d, 1H, J = 15.9), 4.74 (s, 2H),

4.24-4.07 (m, 4H), 1.27 (t, 3H, J = 7.2). LC/MS: LC: retention time 3.99 minutes; MS (APcI): 920.3 (100, [M+H]); calcd $C_{39}H_{28}F_{15}N_3O_6$ [M+H] 920.6.

Example 31

(E)-3-(4-{4-(4-Carboxymethoxy-phenyl)-5-[4-((E)-2-dihexylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-acrylic acid ethyl ester 220



220

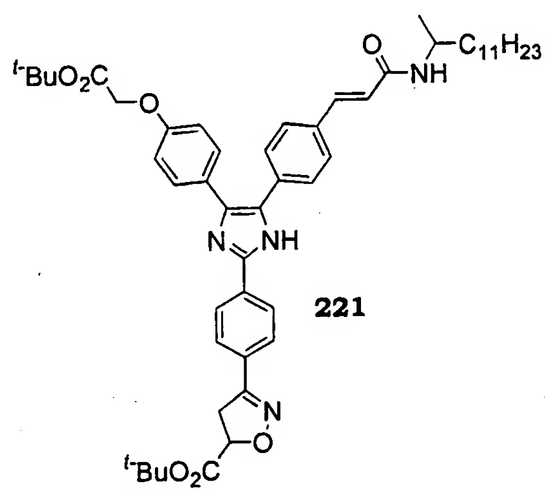
Compound **220** was synthesized according to *General Method 8* from imidazole **56** (400 mg, 0.73 mmol) in DMF (5 mL), with $Pd(OAc)_2$ (33 mg, 0.15 mmol), TEA (203 μL, 1.46 mmol), (*o*-Tolyl)$_3$P (89 mg, 0.29 mmol), and *acrylamide **57g** (210 mg, 0.88 mmol) to give after purification by column chromatograhpy and recrystallization *(E)-3-(4-{4-(4-Carboxymethoxy-phenyl)-5-[4-((E)-2-dihexylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-acrylic acid ethyl ester* **220** as a yellow solid (33 mg, 6.4%). *Acrylamide **57g** was synthesized according to *General Method 9* from acryloyl chloride and dihexylamine.

Data for *(E)-3-(4-{4-(4-Carboxymethoxy-phenyl)-5-[4-((E)-2-dihexylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-acrylic acid ethyl ester* **220**: ^{1}H-NMR

(300 MHz, DMSO-d6): 8.13 (d, 2H, J = 8.4), 7.89 (d, 2H, J = 8.7), 7.71-7.66 (m, 3H), 7.57 (d, 2H, J =7.8), 7.49-7.45 (m, 3H), 7.12 (d, 1H, J = 15.6), 7.01 (d, 2H, J = 8.4), 6.73 (d, 1H, J = 15.9), 4.73 (s, 2H), 4.20 (q, 2H, J = 6.9), 3.44 (t, 2H, J = 4.8), 3.31 (t, 2H, J = 6.9) 1.50 (brs, 4H), 1.26 (s, 15H), 0.84 (d, 6H, J = 6.6). LC/MS: LC: retention time 3.57 minutes; MS (APcI): 706.2 (100, [M+H]); calcd $C_{43}H_{51}N_3O_6$ [M+H] 706.9.

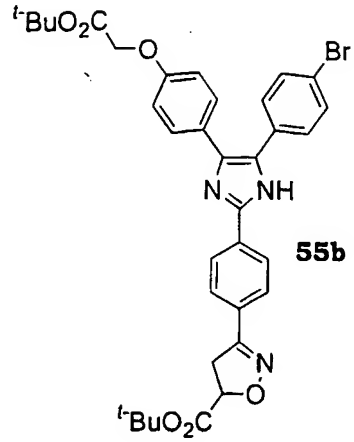
Example 32

3-[4-(4-(4-*tert*-Butoxycarbonylmethoxy-phenyl)-5-{4-[(E)-2-(1-methyl-dodecylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 221



221

Imidazole **55b** was synthesized according to *General Method 7* (Scheme 11) from dione **54** (8.0 g, 19.1 mmol) in acetic acid (20 mL), with 3-(4-Formyl-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester (7.9g, 28.6 mmol) and NH_4OAc (44.2 g, 573 mmol), which gives imidazole **55b** (6.3 g, 49%). Dione **54** was synthesized according to *General Method 4*.



55b

Data for compound **55b** ($R^{1'}$ = *tert*-butyl): ^{1}H-NMR (300 MHz, $CDCl_3$): 7.93 (d, 2H, J = 6.9), 7.64 (d, 2H, J = 7.8), 7.39 (s, 2H), 7.34 (d, 2H, J = 8.1), 6.82 (d, 2H, J = 7.8), 5.06 (t, 1H, J = 8.7), 4.52 (s, 2H), 3.59 (d, 2H, J = 8.1), 1.51 (s, 19H).

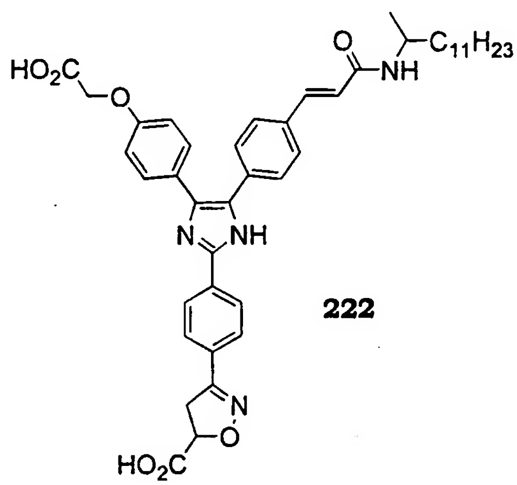
Compound **221** was synthesized according to *General Method 8* from imidazole **55b** (300 mg, 0.44 mmol) in DMF (5 mL), with $Pd(OAc)_2$ (20 mg, 0.09 mmol), TEA (123 µL, 0.88 mmol), (o-Tolyl)$_3$P (54 mg, 0.18 mmol), and *acrylamide **57a** (135 mg, 0.53 mmol) to give, after purification *via* column chromatography eluting with Ethyl Acetate:Hexane followed by recrystallization, *3-[4-(4-(4-tert-Butoxycarbonylmethoxy-phenyl)-5-{4-[(E)-2-(1-methyl-dodecylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **221** as a yellow solid (60 mg, 16%). *Acrylamide **57a** was synthesized according to *General Method 9* from acryloyl chloride and 1-methyl dodecylamine.

Data for *3-[4-(4-(4-tert-Butoxycarbonylmethoxy-phenyl)-5-{4-[(E)-2-(1-methyl-dodecylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **221**: ^{1}H-NMR (300 MHz, $CDCl_3$):

8.07 (d, 2H, J = 7.8), 7.69 (d, 2H, J = 7.8), 7.53-7.43 (m, 5H), 7.33 (d, 2H, J = 8.4), 6.84 (d, 2H, J = 8.4), 6.30 (d, 1H, J = 15.3), 5.69 (brs, 1H), 5.08 (t, 1H, J = 9.3), 4.52 (s, 2H), 4.12-4.06 (m, 1H), 3.59 (d, 2H, J = 9.3), 1.58-1.47 (m, 2H), 1.52 (s, 9H), 1.50 (s, 9H), 1.25 (brs, 18H), 1.17 (d, 3H, J = 6.3), 0.88 (t, 3H, J = 6.6).

Example 33

3-[4-(4-(4-Carboxymethoxy-phenyl)-5-{4-[(E)-2-(1-methyl-dodecylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid 222



222

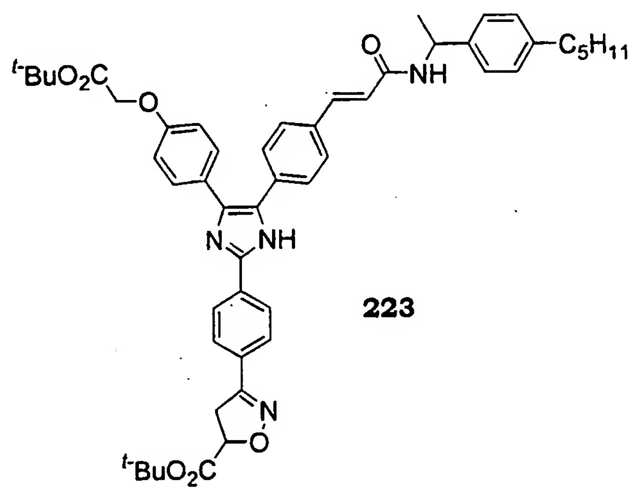
Imidazole **222** was synthesized according to *General Method 11 via* hydrolyses of the *tert*-butyl ester of imidazole **221** according to *General Method 11*, to give *3-[4-(4-(4-Carboxymethoxy-phenyl)-5-{4-[(E)-2-(1-methyl-dodecylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid* **222**, after recrystallization, as a yellow solid (13 mg, 15%).

Data for *3-[4-(4-(4-Carboxymethoxy-phenyl)-5-{4-[(E)-2-(1-methyl-dodecylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-2-yl)-phenyl]-4,5-dihydro-*

isoxazole-5-carboxylic acid **222**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.16 (d, 2H, J = 8.4), 7.80 (d, 2H, J = 8.4), 7.63-7.45 (m, 7H), 7.36 (d, 1H, J =16.5), 7.05-6.89 (m, 2H), 6.67-6.56 (m, 1H), 5.20 (dd, 1H, J = 11.7, 6.9), 4.76-4.69 (m, 2H), 3.87-3.83 (m, 1H), 3.79-3.73 (m, 1H), 3.63 (dd, 1H, J = 6.9, 6.6), 1.40 (bs, 2H) 1.23 (s, 18H), 1.07 (d, 3H, J = 6.6), 0.84 (t, 3H, J = 6.6). LC/MS: LC: retention time 3.24 and 3.42 minutes (micelle aggregation); MS (APcI): 735.6 (100, [M+H]); calcd $C_{43}H_{50}N_4O_7$ [M+H] 735.9.

Example 34

3-{4-[4-(4-*tert*-Butoxycarbonylmethoxy-phenyl)-5-(4-{(E)-2-[1-(4-pentyl-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-1*H*-imidazol-2-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 223



223

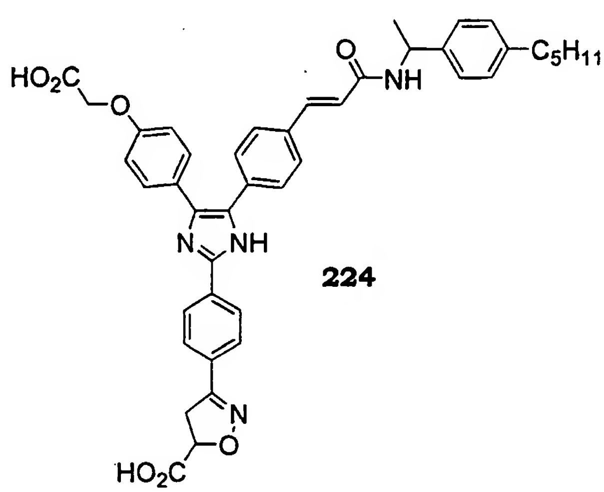
Compound **223** was synthesized according to *General Method 8* from imidazole **55b** (300 mg, 0.44 mmol) in DMF (2.5 mL), with $Pd(OAc)_2$ (20 mg, 0.09 mmol), TEA (123 μL, 0.88 mmol), (*o*-Tolyl)$_3$P (54 mg, 0.18 mmol), and *acrylamide **57d** (130 mg, 0.53 mmol) to give, after purification *via* column chromatography eluting with Ethyl Acetate:Hexane followed by recrystallization, *3-{4-[4-(4-tert-Butoxycarbonylmethoxy-phenyl)-5-(4-{(E)-2-[1-(4-pentyl-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-1H-imidazol-2-yl]-phenyl}-4,5-*

dihydro-isoxazole-5-carboxylic acid tert-butyl ester **223** as a yellow solid (200 mg, 54%). *Acrylamide **57d** was synthesized according to *General Method 9* from acryloyl chloride and 1-(4-pentylphenyl)-ethylamine hydrochloride.

Data for *3-{4-[4-(4-tert-Butoxycarbonylmethoxy-phenyl)-5-(4-{(E)-2-[1-(4-pentyl-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-1H-imidazol-2-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **223**: ^{1}H-NMR (300 MHz, $CDCl_3$): 8.05 (d, 2H, *J* = 7.8), 7.69 (d, 2H, *J* = 8.4), 7.48-7.44 (m, 5H), 7.34-7.21 (m, 4H), 7.14 (d, 2H, *J* = 7.8), 6.84 (d, 2H, *J* = 8.4), 6.31 (d, 1H, *J* = 15.3), 6.13 (brs, 1H), 5.20 (t, 1H, *J* = 6.9), 5.07 (t, 1H, *J* = 9.3), 4.51 (s, 2H), 3.57 (d, 2H, *J* = 9.3), 2.57 (t, 2H, *J* = 7.5) 1.59-1.43 (m, 5H), 1.52 (s, 9H), 1.50 (s, 9H), 1.33-1.30 (m, 4H), 0.83 (t, 3H, *J* = 6.6).

Example 35

3-{4-[4-(4-Carboxymethoxy-phenyl)-5-(4-{(E)-2-[1-(4-pentyl-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-1*H*-imidazol-2-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid 224



224

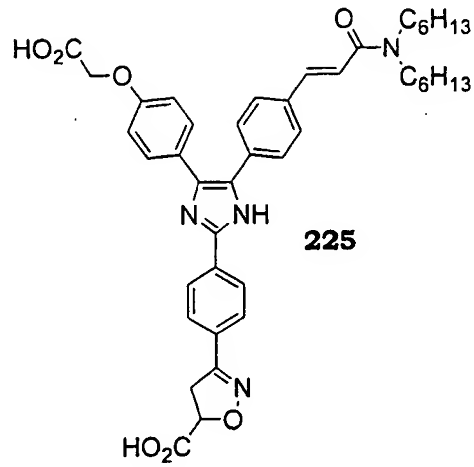
Imidazole **224** was synthesized according to *General Method 11 via* hydrolyses of the *tert*-butyl ester of imidazole **223** according to *General Method 11*, to give *3-{4-[4-(4-Carboxymethoxy-phenyl)-5-(4-{(E)-2-[1-(4-pentyl-*

phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-1H-imidazol-2-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid **224**, after recrystallization, as a pale yellow solid (50 mg, 42%).

Data for *3-{4-[4-(4-Carboxymethoxy-phenyl)-5-(4-{(E)-2-[1-(4-pentyl-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-1H-imidazol-2-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid* **224**: ^{1}H-NMR (300 MHz, $CDCl_3/CD_3OD$): 8.12 (d, 2H, J = 8.7), 8.00 (d, 2H, J = 8.4), 7.66 (d, 2H, J = 8.7), 7.58 (d, 2H, J = 8.7), 7.54 (d, 1H, J = 15.9), 7.50 (d, 2H, J = 8.7), 7.26 (d, 2H, J = 8.4), 7.15 (d, 2H, J = 8.1), 7.08 (d, 1H, J = 8.7), 6.73 (d, 1H, J = 15.9) 5.28 (dd, 1H, J = 11.4, 7.2), 5.11 (q, 1H, J = 6.9), 4.75 (s, 2H), 3.82 (dd, 1H, J = 17.1, 11.4), 3.71 (dd, 1H, J = 17.1, 6.9), 2.58 (t, 2H, J = 7.5) 1.66-1.55 (m, 2H), 1.50 (d, 3H, J = 6.9), 1.40-1.24 (m, 4H), 0.89 (t, 3H, J = 6.6). LC/MS: LC: retention time 2.78 and 3.00 minutes (micelle aggregation); MS (APcI): 727.4 (100, [M+H]); calcd $C_{43}H_{42}N_4O_7$ [M+H] 727.8.

Example 36

3-(4-{4-(4-Carboxymethoxy-phenyl)-5-[4-((E)-2-dihexylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid 225



225

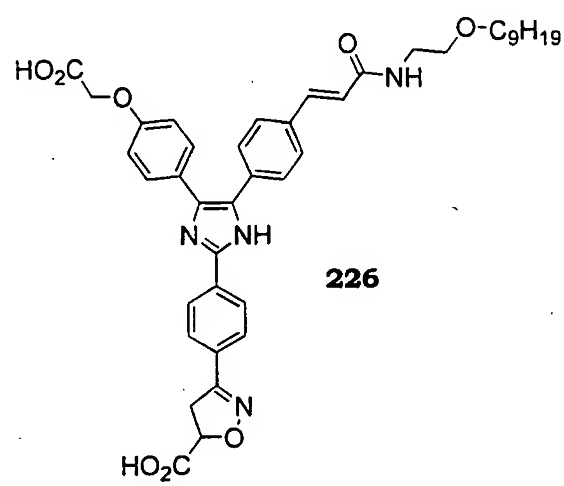
Compound **225** was synthesized according to *General Method 8* from imidazole **55b** (300 mg, 0.44 mmol) in DMF (2.2 mL), with $Pd(OAc)_2$ (20 mg, 0.09 mmol), TEA (123 μL, 0.88 mmol), (*o*-Tolyl)$_3$P (54 mg, 0.18 mmol), and *acrylamide **57g** (127 mg, 0.53 mmol) to give after purification by flash column chromatography followed by recrystallization, 3-(4-{4-(4-*tert*-Butoxycarbonylmethoxy-phenyl)-5-[4-((E)-2-dihexylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester as a yellow solid (300 mg, 80%). *Acrylamide **57g** was synthesized according to *General Method 9* from acryloyl chloride and dihexylamine. The desired imidazole was obtained *via* hydrolyses of the *tert*-butyl esters according to *General Method 11* to give, after recrystallization, *3-(4-{4-(4-Carboxymethoxy-phenyl)-5-[4-((E)-2-dihexylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid* **225** as a yellow solid (70 mg, 19%).

Data for *3-(4-{4-(4-Carboxymethoxy-phenyl)-5-[4-((E)-2-dihexylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid* **225**: ^{1}H-NMR (300 MHz, DMSO-d$_6$): 8.18 (d, 2H, J = 8.1), 7.86 (d, 2H, J = 8.1), 7.72 (d, 2H, J = 8.1), 7.58 (d, 2H, J = 8.4), 7.50-7.45 (m, 3H), 7.03 (d,

1H, $J = 15.6$), 7.01 (d, 2H, $J = 8.4$), 5.22 (dd, 1H, $J = 11.4, 7.2$), 4.74 (s, 2H), 3.84-3.61 (m, 2H), 3.46-3.30 (m, 4H), 1.51 (brs, 4H), 1.27 (s, 12H), 0.86 (d, 6H, $J = 6.3$). LC/MS: LC: retention time 3.63 minute; MS (APcI): 721.5 (100, [M+H]); calcd $C_{42}H_{48}N_4O_7$ [M+H] 721.9.

Example 37

3-[4-(4-(4-Carboxymethoxy-phenyl)-5-{4-[(E)-2-(2-nonyloxy-ethylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid 226



226

Compound **226** was synthesized according to *General Method 8* from imidazole **55b** (300 mg, 0.44 mmol) in DMF (2.2 mL), with $Pd(OAc)_2$ (40 mg, 0.18 mmol), TEA (123 μL, 0.88 mmol), (*o*-Tolyl)$_3$P (107 mg, 0.35 mmol), and *acrylamide **57h** (127 mg, 0.53 mmol) to give after purification by flash column chromatography followed by recrystallization, 3-[4-(4-(4-*tert*-Butoxycarbonylmethoxy-phenyl)-5-{4-[(E)-2-(2-nonyloxy-ethylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester as a yellow solid (139 mg, 38%). *Acrylamide **57h** was synthesized according to *General Method 9* from acryloyl chloride and 2-nonyloxy-ethylamine. The desired imidazole was obtained *via* hydrolyses of

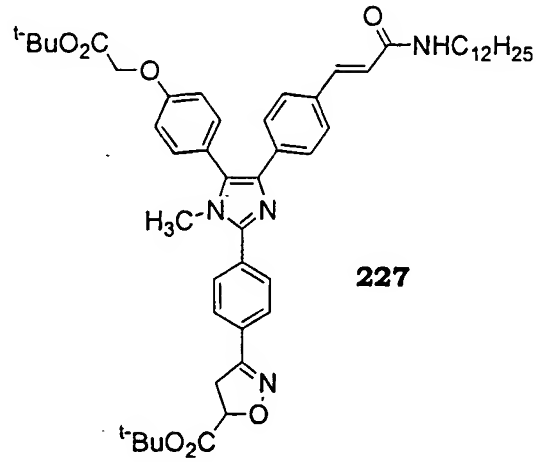
the *tert*-butyl esters according to *General Method 11* to give, after recrystallization, *3-[4-(4-(4-Carboxymethoxy-phenyl)-5-{4-[(E)-2-(2-nonyloxy-ethylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid* **226** as a yellow solid (50 mg, 72%).

Data for *3-[4-(4-(4-Carboxymethoxy-phenyl)-5-{4-[(E)-2-(2-nonyloxy-ethylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid* **226**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.15 (d, 3H, J = 8.4), 7.79 (d, 2H, J = 7.8), 7.63-7.36 (m, 7H), 7.04-6.88 (m, 2H), 6.73-6.61 (m, 1H), 5.19 (dd, 1H, J = 10.5, 6.9), 4.75-4.68 (m, 2H), 3.77 (dd, 1H, J = 17.4, 11.4), 3.63 (dd, 1H, J = 17.7, 7.2), 3.42-3.27 (m, 6H), 1.49 (t, 2H, J = 5.7), 1.23 (s, 12H), 0.83 (t, 3H, J = 5.1). LC/MS: LC: retention time 3.16 minute; MS (APcI): 723.4 (100, [M+H]); calcd $C_{41}H_{46}N_4O_8$ [M+H] 722.8.

Example 38

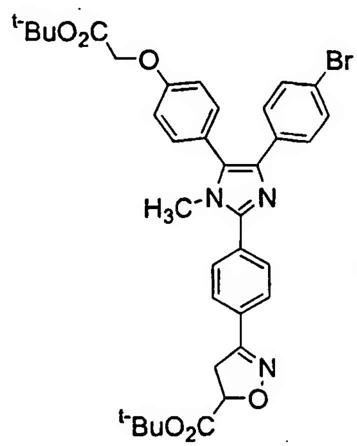
3-(4-{5-(4-*tert*-Butoxycarbonylmethoxy-phenyl)-4-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1-methyl-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester

227



227

To a solution of the imidazole **55b** (equivalent to **135** in Scheme 21) (50 mg, 0.074 mmol) in DMF (150 μL) was added NaH (3.6 mg, 0.15 mmol) in one portion and stirred at r.t. for 20 min. Then, 80 μL of a 1M solution of methyliodide in DMF was added dropwise to the reaction flask. After 3h, the reaction was diluted with ethyl acetate, then washed with water, sat. sodium bicarbonate, sat. sodium chloride, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography eluting with hexane/ethyl acetate (7:3) afforded imidazole **137a** as a white solid (24 mg, 47%).



137a

Data for imidazole **137a**: ^{1}H-NMR (300 MHz, $CDCl_3$): 7.86 (d, 2H, J = 8.1), 7.80 (d, 2H, J = 8.4), 7.43 (d, 2H, J = 8.4), 7.34 (d, 2H, J = 8.4), 7.29 (d, 2H, J = 8.4), 7.01 (d, 2H, J = 8.4), 5.11 (t, 1H, J = 9.3), 4.60 (s, 2H), 3.63 (d, 2H,

J = 9.3), 3.55 (s, 3H), 1.53 (s, 9H), 1.52 (s, 9H). LC/MS: LC: retention time 3.81 minute; MS (APcI): 688.2 (100, [M+H]); calcd $C_{36}H_{38}BrN_3O_6$ [M+H] 688.6.

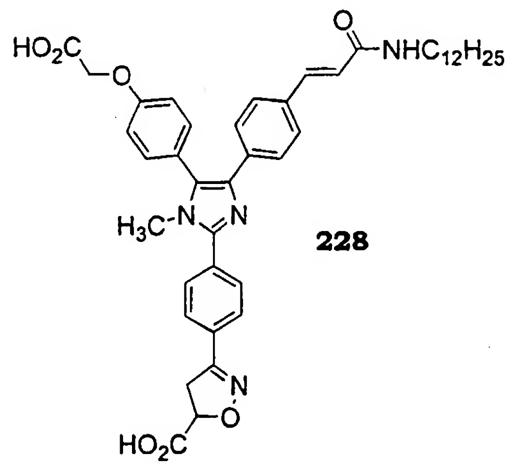
Compound **227** was synthesized according to *General Method 8* from imidazole **137a**. The Br imidazole **137a** (40 mg, 0.058 mmol) was dissolved in DMF (300 μL), followed by addition of $Pd(OAc)_2$ (2.6 mg, 0.012 mmol), TEA (16.2 μL, 0.12 mmol), P-(o-tolyl)$_3$ (7.3 mg, 0.024 mmol) and *acrylamide **57i** (17 mg, 0.07 mmol). The reaction was heated to 100 °C for 2h. The reaction was then quenched with water and extracted with ethyl acetate. The organic layer was washed with water, sat. sodium chloride, dried under $MgSO_4$, filtered and concentrated to give a yellow oil. The oil was purified by flash column chromatography eluting with hexane/ethyl acetate (7:3) to give *3-(4-{5-(4-tert-Butoxycarbonylmethoxy-phenyl)-4-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1-methyl-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **227** as a light yellow solid (20 mg, 41%). *acrylamide **57i** was synthesized according to *General Method 9* from acryloyl chloride and dodecylamine.

Data for *3-(4-{5-(4-tert-Butoxycarbonylmethoxy-phenyl)-4-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1-methyl-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **227**: ^{1}H-NMR (300 MHz, $CDCl_3$): 7.85 (d, 2H, J = 8.7), 7.81 (d, 2H, J = 8.4), 7.56-7.50 (m, 3H), 7.35-7.31 (m, 4H), 7.02 (d, 2H, J = 8.7), 6.34 (d, 1H, J = 15.6), 5.74 (brs, 1H), 5.11 (t, 1H, J = 9.3), 4.60 (s, 2H), 3.63 (d, 2H, J = 9.3), 3.54 (s, 3H), 3.36 (q, 2H, J

= 6.6), 1.53-1.52 (m, 20H), 1.26 (brs, 18H), 0.88 (t, 3H, J = 6.0). LC/MS: LC: retention time 4.67 minute; MS (APcI): 848.0 (100, [M+H]); calcd $C_{51}H_{66}N_4O_7$ [M+H] 848.1.

Example 39

3-(4-{5-(4-Carboxymethoxy-phenyl)-4-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1-methyl-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid 228



228

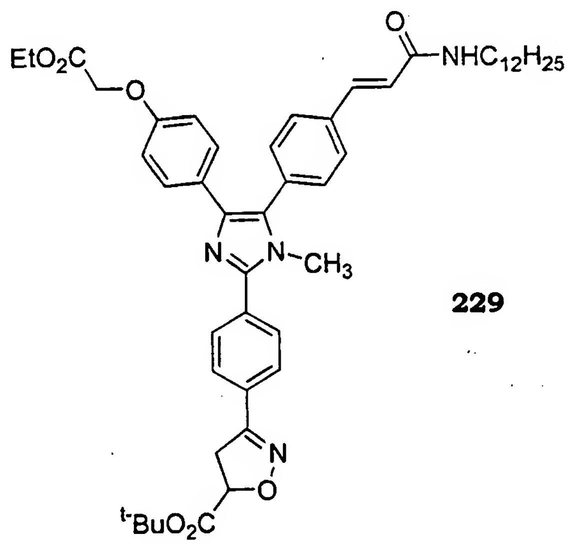
The t-butyl ester **226** was hydrolyzed according to *General Method 11* to give, after recrystallization, the desired imidazole *3-(4-{5-(4-Carboxymethoxy-phenyl)-4-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1-methyl-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid* **228** as a yellow solid (33 mg, 77%).

Data for *3-(4-{5-(4-Carboxymethoxy-phenyl)-4-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1-methyl-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid* **228**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.07 (t, 1H, J = 5.1), 7.96 (s, 4H), 7.54 (d, 2H, J = 8.7), 7.47 (d, 2H, J = 8.4), 7.44 (d, 2H, J = 8.4) 7.36 (d, 1H, J = 15.6), 7.13 (d, 2H, J = 8.4), 6.60 (d, 1H, J = 15.6), 5.26 (dd, 1H, J

= 11.7, 6.9), 4.79 (s, 2H), 3.82 (dd, 1H, J = 16.8, 12.0), 3.71 (dd, 1H, J = 17.4, 7.2), 3.56 (s, 3H), 3.12 (q, 2H, J = 6.3), 1.43 (t, 2H, J = 5.4), 1.24 (s, 18H), 0.84 (t, 3H, J = 6.3). LC/MS: LC: retention time 3.69 minute; MS (APcI): 735.4 (100, [M+H]); calcd $C_{43}H_{50}N_4O_7$ [M+H] 735.9.

Example 40

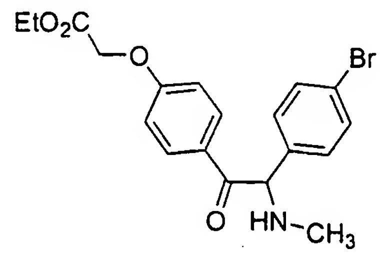
3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-(4-ethoxycarbonylmethoxy-phenyl)-1-methyl-1*H*-imidazol-2-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 229



229

To a solution of the α-keto bromide **130** (R^1 = Et) (207 mg, 0.45 mmol) in 1,4 dioxane (0.5 mL) and DMSO (0.5 mL), was added methylamine hydrochloride (31 mg, 0.45 mmol) and DIEA (117 μL, 0.68 mmol). The reaction was stirred at 0 °C for 1h (Scheme 20). After 1h, the reaction was removed from the ice bath and stirred at r.t. for 16h. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water, sat. sodium chloride, dried under $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by flash column

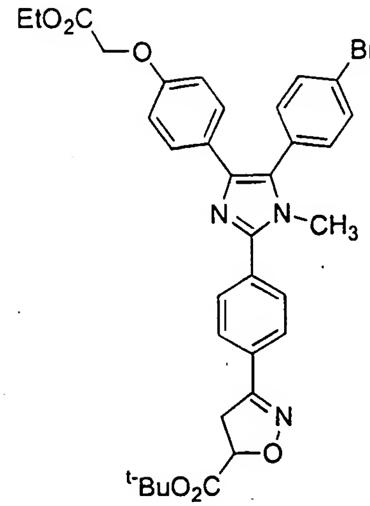
chromatography eluting with hexane/ethyl acetate (1:1) to afford the desired compound **132a** as a light yellow oil (70 mg, 38%).



132a

Data for Compound **132a**: ^{1}H-NMR (300 MHz, $CDCl_3$): 7.92 (d, 2H, J = 8.7), 7.45 (d, 2H, J = 8.1), 7.21 (d, 2H, J = 8.4), 6.89 (d, 2H, J = 8.7), 5.11 (s, 1H), 4.65 (s, 2H), 4.27 (q, 2H, J = 7.2), 2.39 (s, 3H), 1.29 (t, 3H, J = 6.9). LC/MS: LC: retention time 4.12 minute; MS (APcI): 377.2 (100, [M+H-CH_2CH_3]); calcd $C_{19}H_{20}BrNO_4$ [M+H] 407.3.

The imidazole **134a** was prepared from **132a** according to *General Method 7.* Acetic acid (1 mL) was added to a mixture of the α-keto methylamine **132a** (65 mg, 0.16 mmol), 3-(4-Formyl-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester (66 mg, 0.24 mmol), and NH_4OAc (370 mg, 4.8 mmol) and heated to 100 °C for 2h. The reaction mixture was quenched with ice water, extracted with ethyl acetate (20 mL x 2). The organic layer was washed with water, sat. sodium chloride, dried under $MgSO_4$, filtered and concentrated *in vacuo.* The crude mixture was purified by flash column chromatography eluting with hexane/ethyl acetate (6:4) to afford the desired compound **134a** (40 mg, 38%).



134a

Data for Compound **134a**: ^{1}H-NMR (300 MHz, $CDCl_3$): 7.84-7.77 (m, 4H), 7.61 (d, 2H, J = 8.1), 7.46 (d, 2H, J = 9.0), 7.27 (d, 2H, J = 8.4), 7.80 (d, 2H, J = 8.7), 5.10 (t, 1H, J = 9.3), 4.59 (s, 2H), 4.26 (q, 2H, J = 7.2), 3.63 (d, 2H, J = 9.3), 3.54 (s, 3H), 1.52 (s, 9H), 1.29 (t, 3H, J = 6.9).

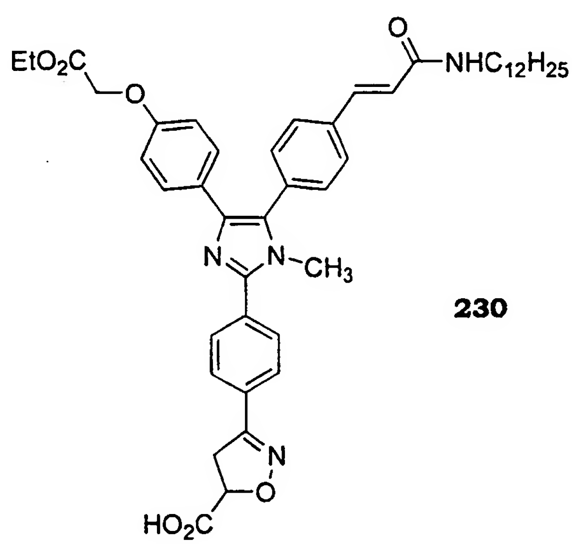
Compound **229** was prepared as described in *General Method 8* from the intermediate **134a**. The Br imidazole **134a** (260 mg, 0.39 mmol) was dissolved in DMF (0.9 mL), followed by addition of $Pd(OAc)_2$ (35 mg, 0.16 mmol), TEA (109 μL, 0.78 mmol), P-(o-tolyl)$_3$ (95 mg, 0.31 mmol) and acrylamide **57i** (113 mg, 0.47 mmol). The reaction was heated to 100 C for 2h. The reaction was then quenched with water and extracted with ethyl acetate. The organic layer was washed with water, sat. sodium chloride, dried under $MgSO_4$, filtered and concentrated to give a yellow residue. The oil was purified by flash column chromatography eluting with hexane/ethyl acetate/dichloromethane to afford a light yellow solid (200 mg, 63%). Recrystallizing with ethyl acetate/hexane, filtering of the solids and rinsing with ether gave *3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-(4-ethoxycarbonylmethoxy-phenyl)-1-methyl-1H-imidazol-2-yl]-phenyl}-4,5-*

dihydro-isoxazole-5-carboxylic acid tert-butyl ester **229** as a light yellow solid (167 mg, 84%).

Data for *3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-(4-ethoxycarbonylmethoxy-phenyl)-1-methyl-1H-imidazol-2-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **229**: ^{1}H-NMR (300 MHz, $CDCl_3$): 7.92 (d, 2H, J = 6.9), 7.79 (d, 2H, J = 8.1), 7.66 (d, 1H, J = 15.6), 7.57 (d, 2H, J = 7.5), 7.50 (d, 2H, J = 8.7), 7.32 (d, 2H, J = 7.8), 7.80 (d, 2H, J = 8.7), 6.49 (d, 1H, J = 15.9), 5.83 (brs, 1H), 5.13 (t, 1H, J = 9.0), 4.59 (s, 2H), 4.27 (q, 2H, J = 7.2), 3.64 (d, 2H, J = 3.3), 3.60 (s, 3H), 3.41 (q, 2H, J = 6.6), 1.57-1.51 (m, 11H), 1.32-1.27 (m, 21H), 0.89 (t, 3H, J = 6.3).

Example 41

3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-(4-ethoxycarbonylmethoxy-phenyl)-1-methyl-1*H*-imidazol-2-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid 230



230

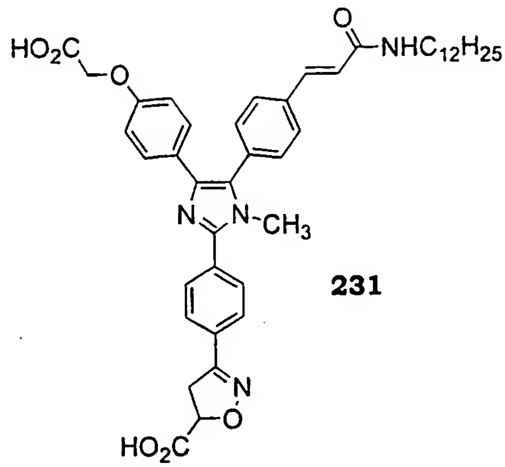
Compound **230** was prepared according to *General Method 11* from **229** (186 mg, 0.24 mmol). Purification *via* flash column chromatography

eluting with 2% methanol/dicholoromethane with 1% formic acid afforded *3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-(4-ethoxycarbonylmethoxy-phenyl)-1-methyl-1H-imidazol-2-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid* **230** as a yellow solid (100 mg, 54%).

Data for *3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-(4-ethoxycarbonylmethoxy-phenyl)-1-methyl-1H-imidazol-2-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid* **230**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.12 (t, 1H, J = 6.0), 7.90 (dd, 2H, J = 8.7), 7.84 (d, 2H, J = 8.7), 7.11 (d, 2H, J = 8.4), 7.49 (d, 3H, J = 8.1), 7.37 (d, 2H, J = 8.7), 6.83 (d, 2H, J = 8.7), 6.70 (d, 1H, J = 15.9), 5.22 (dd, 1H, J = 11.7, 6.6), 4.73 (s, 2H), 4.14 (q, 2H, J = 6.9), 3.80 (dd, 1H, J = 16.8, 11.4), 3.65 (dd, 1H, J = 17.4, 7.2), 3.54 (s, 3H), 3.18 (q, 2H, J = 6.6), 1.46 (t, 2H, J = 7.5), 1.24 (brs, 18H), 1.19 (t, 3H, J = 7.2), 0.85 (t, 3H, J = 6.6). LC/MS: LC: retention time 3.95 minute; MS (APcI): 763.5 (100, [M+H]); calcd $C_{45}H_{54}N_4O_7$ [M+H] 763.9.

Example 42

3-(4-{4-(4-Carboxymethoxy-phenyl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1-methyl-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid 231



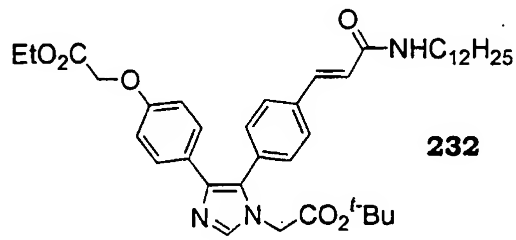
231

Compound **231** was prepared according to *General Method 10* from imidazole **230** (40 mg, 0.052 mmol) after workup to obtain *3-(4-{4-(4-Carboxymethoxy-phenyl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1-methyl-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid* **231** as a light yellow solid (31 mg, 82%).

Data for *3-(4-{4-(4-Carboxymethoxy-phenyl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1-methyl-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid* **231**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.13 (t, 1H, J = 5.7), 7.90 (d, 2H, J = 8.7), 7.85 (d, 2H, J = 8.4), 7.70 (d, 2H, J = 8.1), 7.49 (d, 2H, J = 8.7) 7.48 (d, 1H, J = 14.7), 7.36 (d, 2H, J = 8.4), 6.81 (d, 2H, J = 8.4), 6.70 (d, 1H, J = 15.9), 5.22 (dd, 1H, J = 11.7, 6.9), 4.63 (s, 2H), 3.80 (dd, 1H, J = 17.1, 11.7), 3.65 (dd, 1H, J = 17.1, 7.2), 3.55 (s, 3H), 3.18 (q, 2H, J = 6.3), 1.46 (t, 2H, J = 5.7), 1.24 (s, 18H), 0.85 (t, 3H, J = 6.3). LC/MS: LC: retention time 3.63 minute; MS (APcI): 734.9 (100, [M+H]); calcd $C_{43}H_{50}N_4O_7$ [M+H] 734.9.

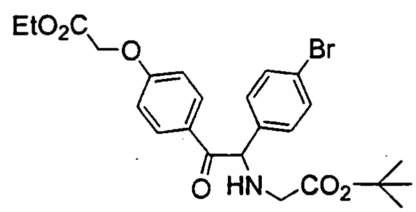
Example 43

[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-(4-ethoxycarbonylmethoxy-phenyl)-imidazol-1-yl]-acetic acid *tert*-butyl ester 232



232

α-keto bromide **130** (R^1 = Et) (4.1 g, 8.99 mmol) (synthesized according to *General Method 13*)was dissolved in 1,4-Dioxane (10 mL) and DMSO (10 mL). Glycine *tert*-butyl ester(1.6 g, 13.48 mmol) was added. After the mixture was stirred at RT for 2h, water (50 mL) was introduced. The reaction was extracted with ethyl acetate (3 x 50 mL) and the combined organic portions were washed by water, brine, dried under magnesium sulfate, filtered, and concentrated to dryness *in vacuo*. Purification *via* flash column chromatography afforded the desired product **132b** (1.86 g, 40.8%).

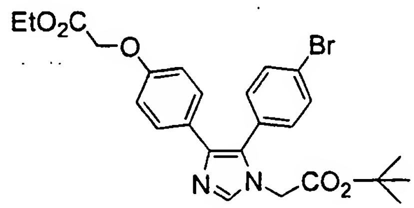


132b

Data for **132b**: ^{1}H-NMR (300 MHz, $CDCl_3$): 7.95 (d, 1H, J = 8.4), 7.45 (d, 2H, J = 8.4), 7.25 (d, 2H, J = 8.4), 6.90 (d, 2H, J = 8.4), 5.40 (s, 1H), 4.65 (s, 2H), 4.30 (q, 2H, J =7.2), 3.30 (s, 2H), 3.00 (brs, 1H), 1.50 (s, 9H), 1.31 (t, 3H, J = 7.2).

Compound **132b** (1.86 g, 3.67 mmol), hexamethylenetetramine (2.57 g, 18.4 mmol), and NH_4OAc (8.49 g, 110.2 mmol) were dissolved in acetic acid (15 mL). The mixture was stirred at 100 C for 1h, then poured into ice

water and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with water (3 x 100 mL), brine (2 x 100 mL) and dried under magnesium sulfate. After filtration, the clear solution was dried under vacuum. The crude product was purified by silica gel chromatography. The imidazole **134b** was obtained (0.54 g, 28%).



134b

Data for **134b**: ^{1}H-NMR (300 MHz, $CDCl_3$): 7.62 (s, 1H), 7.57 (d, 2H, J = 8.7), 7.40 (d, 2H, J = 9.3), 7.19 (d, 2H, J = 8.1), 6.78 (d, 2H, J = 9.0), 4.59 (s, 2H), 4.40 (s, 2H), 4.26 (q, 2H, J = 7.2), 1.40 (s, 9H), 1.28 (t, 3H, J = 7.2).

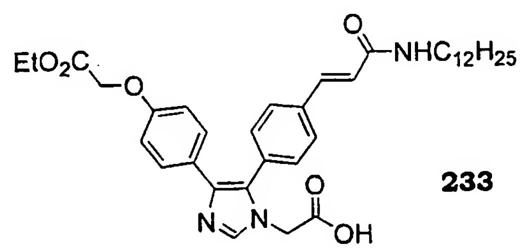
Compound **134b** (0.54 g, 1.05 mmol) was dissolved in DMF (10 mL), followed by addition of $Pd(OAc)_2$ (0.024 g, 0.1 mmol), TEA (0.44 mL, 3.14 mmol), P-(o-tolyl)$_3$ (0.032 g, 0.1 mmol) and acrylamide **57i** (0.3 g, 1.26 mmol). The reaction mixture was heated for 100 °C for 2h. The reaction was quenched *via* addition of water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic portions were washed with 1N HCl (aq.), water, dried under magnesium sulfate, filtered and concentrated *in vacuo*. The crude was purified by silica gel chromatography to give the desired product *[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-(4-ethoxycarbonylmethoxy-phenyl)-imidazol-1-yl]-acetic acid tert-butyl ester* **232** (0.34 g, 48%).

Data for *[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-(4-ethoxycarbonylmethoxy-phenyl)-imidazol-1-yl]-acetic acid tert-butyl ester* **232**:

^{1}H-NMR (300 MHz, CDCl3): 7.63 (d, 1H, J = 15.3), 7.60 (s, 1H), 7.50 (d, 2H, J = 8.1), 7.38 (d, 2H, J = 8.7), 7.26 (d, 2H, J = 8.4), 6.74 (d, 2H, J =8.7), 6.44 (d, 1H, J =15.3), 5.97 (t, 1H, J = 5.5), 4.55 (s, 2H), 4.40 (s, 2H), 4.22 (q, 2H, J = 7.2), 3.40-3.34 (m, 2H), 1.60-1.51 (br, m, 2H), 1.35 (s, 9H), 1.30-1.22 (br, m, 21H), 0.86 (t, 3H, J = 6.7).

Example 44

[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-(4-ethoxycarbonylmethoxy-phenyl)-imidazol-1-yl]-acetic acid 233



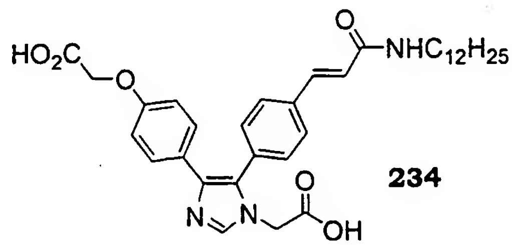
233

Hydrolysis of imidazole **232** according to *General Method 11* gave, after recrystallization *[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-(4-ethoxycarbonylmethoxy-phenyl)-imidazol-1-yl]-acetic acid* **233** as a white solid (0.24 g, 70%).

Data for *[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-(4-ethoxycarbonylmethoxy-phenyl)-imidazol-1-yl]-acetic acid* **233**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.83 (br s, 1H), 8.14 (t, 1H, J = 5.4), 7.69 (d, 2H, J = 8.4), 7.46 (d, 1H, J = 15.9), 7.38 (d, 2H, J = 8.1), 7.29 (d, 2H, J = 8.7), 6.91 (d, 2H, J =8.4), 6.70 (d, 1H, J =15.6), 4.86 (br s, 2H), 4.77 (s, 2H), 4.14 (q, 2H, J = 7.2), 3.20-3.13 (m, 2H), 1.50-1.40 (br, m, 2H), 1.24 (br s, 18H), 1.19 (t, 3H, J = 7.2), 0.85 (t, 3H, J = 6.3). MS (APcI): 618.4 (100, [M+H]); calcd $C_{36}H_{48}N_3O_6$ [M+H] 618.4.

Example 45

{4-(4-Carboxymethoxy-phenyl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-imidazol-1-yl}-acetic acid 234



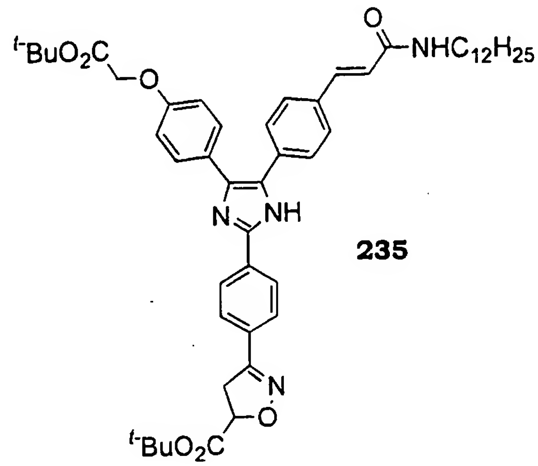
234

Imidazole **233** (0.067 g, 0.1 mmol) was dissolved in 1,4-Dioxane (1 mL) and 1N LiOH (1 mL, 1 mmol) was added. The reaction was stirred at RT for 2h, acidified with 1N HCl (2 mL) and extracted with chloroform. After recrystallization, the desired product *{4-(4-Carboxymethoxy-phenyl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-imidazol-1-yl}-acetic acid* **234** was obtained (0.035 g, 52%).

Data for *{4-(4-Carboxymethoxy-phenyl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-imidazol-1-yl}-acetic acid* **234**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.14 (s, 1H), 8.13 (t, 1H, J = 6.6), 7.65 (d, 2H, J = 7.8), 7.45 (d, 1H, J = 15.6), 7.33 (d, 2H, J = 7.8), 7.29 (d, 2H, J = 8.7), 6.81 (d, 2H, J =8.7), 6.68 (d, 1H, J =15.6), 4.73 (br s, 2H), 4.62 (s, 2H), 3.20-3.13 (m, 2H), 1.50-1.40 (br, m, 2H), 1.24 (br s, 18H), 0.84 (t, 3H, J = 6.3). MS (APcI): 590.4 (100, [M+H]); calcd for $C_{34}H_{44}N_3O_6$ [M+H] 590.3.

Example 46

3-(4-{4-(4-*tert*-Butoxycarbonylmethoxy-phenyl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 235



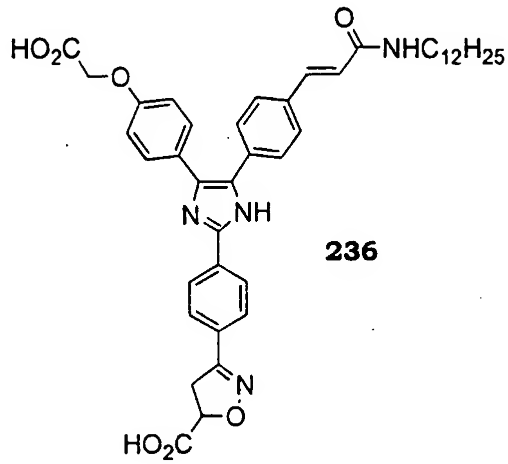
235

Compound **235** was synthesized according to *General Method 7* from dione **59a** ($R^{1'}$ = *t*-butyl, $R^{2'}$ = $C_{12}H_{25}$) (0.3 g, 0.52 mmol) in acetic acid (3 mL), 3-(4-Formyl-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester (0.17 g, 0.62 mmol) and NH_4OAc (1.2 g, 15.6 mmol), which gives, after purification *via* column chromatography eluting with methanol/DCM, *3-(4-{4-(4-tert-Butoxycarbonylmethoxy-phenyl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **235** (0.22 g, 50.7%).

Data for *3-(4-{4-(4-tert-Butoxycarbonylmethoxy-phenyl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **235**: ^{1}H-NMR (300 MHz, $CDCl_3$): 8.12 (d, 2H, J = 8.1), 7.65 (d, 2H, J = 8.4), 7.50-7.38 (m, 5H), 7.25 (d, 2H, J = 8.1), 6.79 (d, 2H, J = 8.7), 6.31 (d, 1H, J =15.9), 5.08 (t, 1H, J = 8.7), 4.49 (s, 2H), 3.57 (d, 2H, J =8.7), 3.38-3.28 (m, 2H), 1.52 (s, 9H), 1.52-1.44 (br, s, 11H), 1.25 (br, s, 18H), 0.88 (t, 3H, J = 6.6).

Example 47

<u>3-(4-{4-(4-Carboxymethoxy-phenyl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid</u> 236



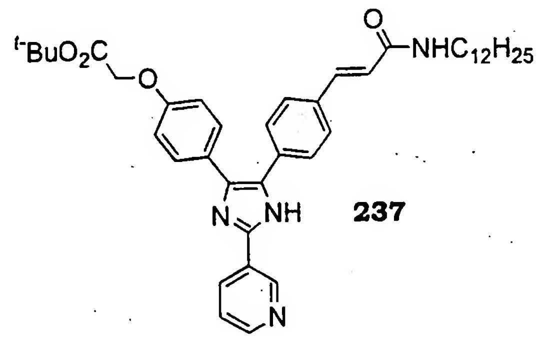
236

The *t*-butyl ester of imidazole **235** was hydrolyzed according to *General Method 11* to give, after recrystallization, the desired imidazole *3-(4-{4-(4-Carboxymethoxy-phenyl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid* **236** as a yellow solid (0.12 g, 50%).

Data for *3-(4-{4-(4-Carboxymethoxy-phenyl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid* **236**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.20 (d, 2H, J = 8.7), 8.11 (t, 1H, J = 5.7), 7.93 (d, 2H, J = 8.1), 7.63 (d, 2H, J = 8.7), 7.58 (d, 2H, J = 8.4), 7.48 (d, 2H, J =8.4), 7.42 (d, 1H, J = 15.6), 7.05 (d, 2H, J =9.0), 6.66 (d, 1H, J =15.9), 5.24 (dd, 1H, J =11.7, 6.9), 4.76 (s, 2H), 3.85-3.62 (m, 2H), 3.22-3.11 (m, 2H), 1.50-1.40 (br, m, 2H), 1.24 (br s, 18H), 0.85 (t, 3H, J = 6.6). MS (APcI): 721.4 (100, [M+H]), 649.5 (60), 633.3 (60); calcd $C_{42}H_{49}N_4O_7$ [M+H] 721.4.

Example 48

(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-pyridin-3-yl-1*H*-imidazol-4-yl}-phenoxy)-acetic acid *tert*-butyl ester 237



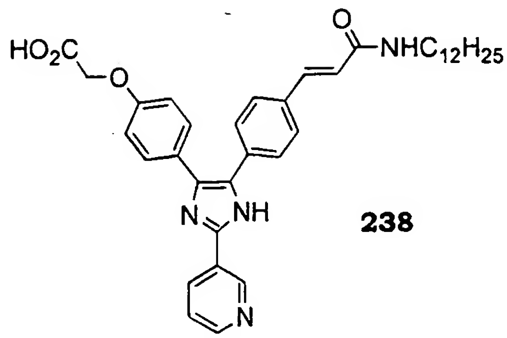
237

Compound **237** was synthesized according to *General Method 7* from dione **59a** ($R^{1'}$ = *t*-butyl, $R^{2'}$ = $C_{12}H_{25}$) (0.3 g, 0.52 mmol) in acetic acid (3 mL), 4-pyridinecarboxaldehyde (0.06 mL, 0.62 mmol) and NH_4OAc (1.2 g, 15.6 mmol), which gives *(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-pyridin-3-yl-1H-imidazol-4-yl}-phenoxy)-acetic acid tert-butyl ester* **237** (0.2 g, 57.8%).

Data for *(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-pyridin-3-yl-1H-imidazol-4-yl}-phenoxy)-acetic acid tert-butyl ester* **237**: ^{1}H-NMR (300 MHz, $CDCl_3$): 9.20 (br s, 1H), 8.58 (br, d, 1H, J = 4.8), 8.37 (br, d, 1H, J = 7.8), 7.62-7.33 (m, 8H), 6.86 (d, 2H, J =9.0), 6.31 (d, 1H, J =15.3), 5.81 (br s, 1H), 4.53 (s, 2H), 3.38-3.31 (m, 2H), 1.59-1.46 (br, m, 11H), 1.26 (br s, 18H), 0.88 (t, 3H, J = 6.7).

Example 49

(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-pyridin-3-yl-1*H*-imidazol-4-yl}-phenoxy)-acetic acid 238



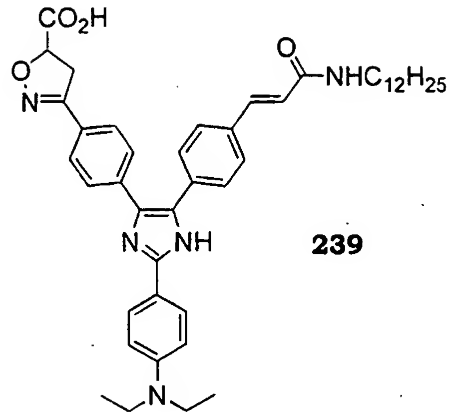
238

Compound **237** was hydrolyzed according to *General Method 11* to give, after recrystallization from ethyl acetate/methanol, the desired imidazole *(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-pyridin-3-yl-1H-imidazol-4-yl}-phenoxy)-acetic acid* **238** as a yellow solid (0.06 g, 30%).

Data for *(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-pyridin-3-yl-1H-imidazol-4-yl}-phenoxy)-acetic acid* **238**: ^{1}H-NMR (300 MHz, DMSO-d_6): 9.31 (br s, 1H), 8.68 (br s, 1H), 8.52 (br, d, 1H, J = 7.8), 8.11 (t, 1H, J = 7.5), 7.68-7.56 (m, 5H), 7.48 (d, 2H, J =8.4), 7.41 (d, 1H, J =15.9), 7.02 (d, 2H, J =8.7), 6.63 (d, 1H, J =15.9), 4.74 (s, 2H), 3.20-3.15 (m, 2H), 1.50-1.40 (br, m, 2H), 1.24 (br s, 18H), 0.84 (t, 3H, J = 6.6). MS (APcI): 609.2 (100, [M+H]); calcd $C_{37}H_{45}N_4O_4$ [M+H] 609.3

Example 50

3-(4-{2-(4-Diethylamino-phenyl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid 239

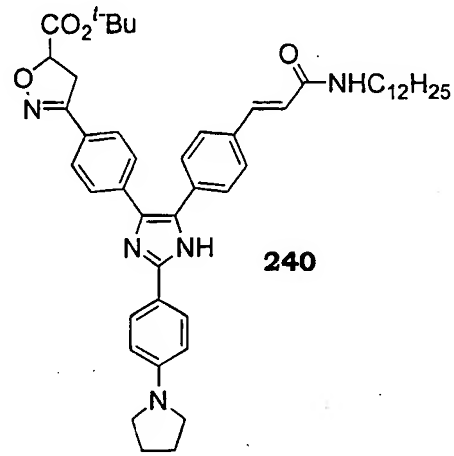


239

Compound **239** was synthesized according to *General Method 7* from dione **46j** (0.054 g, 0.095 mmol) in acetic acid (1 mL) with 4-diethylaminobenzaldehyde (0.020 g, 0.105 mmol) and NH_4OAc (0.22 g, 2.85 mmol). The resulting imidazole was purified by flash column chromatography eluting with hexane/ethyl acetate (3:1). The desired precursor imidazole *3-(4-{2-(4-Diethylamino-phenyl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester* was obtained as a yellow solid (0.032 g, 44%). The methyl ester was hydrolyzed according to *General Method 10* to give, after recrystallization, the desired imidazole *3-(4-{2-(4-Diethylamino-phenyl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid* **239** as a yellow solid (0.02 g, 62%). Data for *3-(4-{2-(4-Diethylamino-phenyl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid* **239**: ^{1}H-NMR (300 MHz, CD_3OD): 8.30-7.60 (m, 11H), 7.01 (d, 2H, J = 7.0), 6.82 (d, 1H, J=15.9), 5.30-5.20 (m, 1H), 4.00-3.40 (m, 8H), 1.85-1.70 (m, 2H), 1.65-1.30 (m, 24H), 1.25-1.00 (m, 3H).

Example 51

3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-(4-pyrrolidin-1-yl-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 240



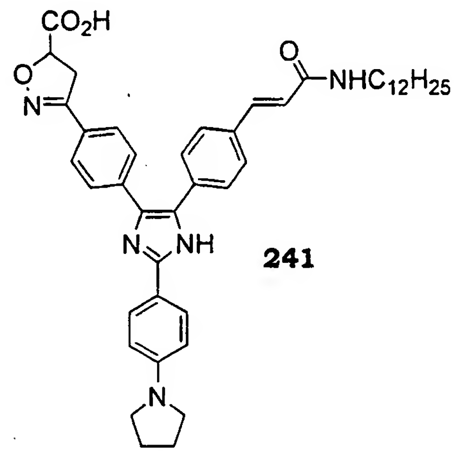
240

Compound **240** was synthesized according to *General Method 7* from dione ***46b*** (1.2 g, 1.95 mmol) in acetic acid (15 mL), with 4-pyrrolidin-1-yl-benzaldehyde (0.38 g, 2.14 mmol) and NH_4OAc (4.5 g, 58.5 mmol), which gives, after purification *via* column chromatography eluting with Methanol/DCM, *3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-(4-pyrrolidin-1-yl-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **240**.

Data for *3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-(4-pyrrolidin-1-yl-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **240**: ^{1}H-NMR (400 MHz, $CDCl_3$: 7.88 (d, 2H, J = 8.4), 7.60-7.50 (br, m, 4H), 7.46-7.36 (br, m, 3H), 7.31 (d, 2H, J = 8.4), 6.58 (d, 2H, J = 8.4), 6.28 (d, 1H, J = 15.6), 6.05 (br,s 1H), 5.06-5.01 (m, 1H), 3.58-3.51 (m, 2H), 3.45 (m, 2H, 2.05 (br, s, 4H), 1.50 (br s, 11H), 1.30 (br, s, 18H), 0.85 (t, 3H, J = 7.5).

Example 52

3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-(4-pyrrolidin-1-yl-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid 241



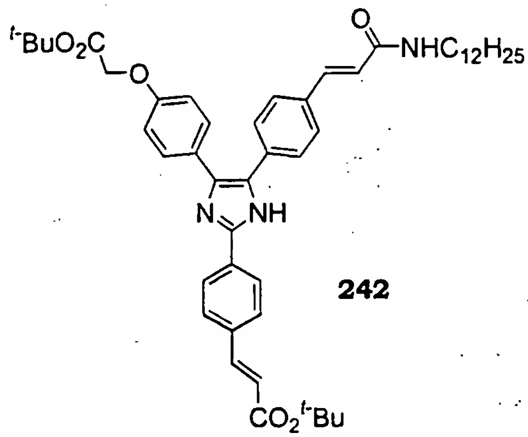
241

The *tert*-butyl ester of **240** was hydrolyzed according to *General Method 11* to give, after recrystallization, the desired imidazole *3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-(4-pyrrolidin-1-yl-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid* **241** as a yellow solid (0.4 g, 29%).

Data for *Dodecylcarbamoyl-vinyl)-phenyl]-2-(4-pyrrolidin-1-yl-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid* **241**: ^{1}H-NMR (300 MHz, DMSO-d$_6$): 8.07 (t, 1H, J = 5.7), 7.90 (d, 2H, J = 9.0), 7.69 (d, 2H, J = 8.1), 7.62-7.56 (m, 6H), 7.41 (d, 1H, J = 15.6), 6.65-6.60 (m, 3H), 5.20-5.14 (m, 1H), 3.79-3.54 (m, 2H), 3.30 (br, s, 4H), 3.19-3.13 (m, 2H), 1.98 (br, s, 4H), 1.50-1.40 (br, m, 2H), 1.24 (br, s, 18H), 0.85 (t, 3H, J = 7.5). MS (ESI): 716.8 (100, [M+H]); calcd for $C_{44}H_{53}N_5O_4$ [M+H] 716.4.

Example 53

(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-[4-((E)-2-*tert*-butoxycarbonyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenoxy)-acetic acid *tert*-butyl ester 242



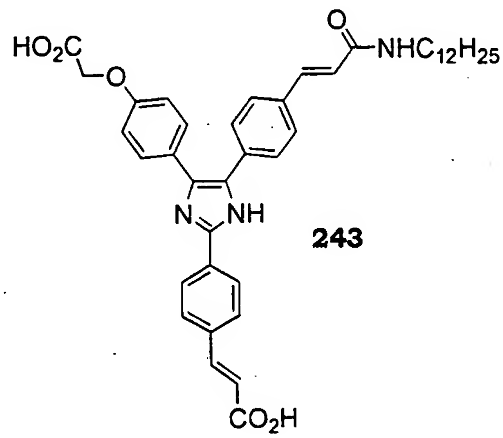
242

Compound **242** was synthesized according to *General Method 7* from dione **59a** ($R^{1'}$ = ^{t}Bu, $R^{2'}$ = $C_{12}H_{25}$) (0.100 g, 0.17 mmol) in acetic acid (2 mL), 4-formylcinnamic acid *tert*-butyl ester (0.044 g, 0.19 mmol) and NH_4OAc (0.400 g, 5.2 mmol). The resulting imidazole was purified by flash column chromatography eluting with 2%methanol in DCM. The desired imidazole *(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-[4-((E)-2-tert-butoxycarbonyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenoxy)-acetic acid tert-butyl ester* **242** was obtained as a yellow solid (27 mg, 20%).

Data for *(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenoxy)-acetic acid* **242**: ^{1}H-NMR (300 MHz, $CDCl_3$): 8.07 (d, 2H, J = 7.5), 7.67-7.36 (m, 8H), 7.29 (d, 2H, J = 7.8), 6.82 (d, 2H, J = 7.5), 6.35 (d, 1H, J = 17.1), 6.30 (d, 1H, J = 16.8), 6.11 (br s, 1H), 4.51 (s, 2H), 3.38-3.24 (m, 2H), 1.65-1.45 (m, 2H), 1.55 (s, 9H), 1.50 (s, 9H), 1.25 (br s, 18H), 0.89 (t, 3H, J = 6.6); MS (APcI): 789.9 (100, [M]), 791.6 (63, [M+H]); calcd $C_{41}H_{48}N_3O_6$ ([M]) 790.0.

Example 54

(4-{2-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenoxy)-acetic acid 243



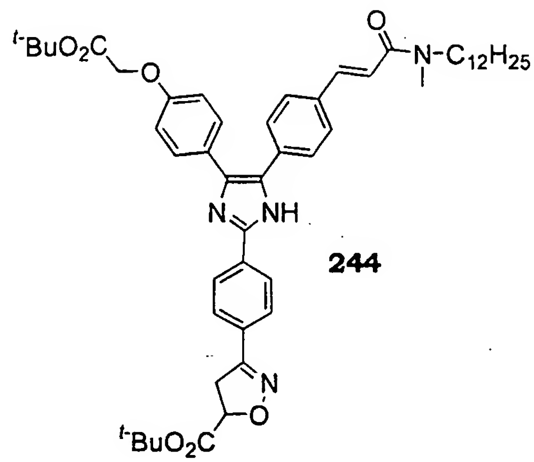
243

The *tert*-butyl esters of imidazole **242** were hydrolyzed according to *General Method 11* to give imidazole **243**. After recrystallization from methanol/ethyl acetate, *(4-{2-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenoxy)-acetic acid* **243** 55 mg, (80%), was obtained as a yellow solid.

Data for *(4-{2-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenoxy)-acetic acid* **243**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.12 (d, 2H, J = 8.4), 8.07 (t, 1H, J = 5.1), 7.85 (d, 2H, J = 7.8), 7.62 (d, 1H, J = 15.9), 7.57 (s, 4H), 7.46 (d, 2H, J = 8.7), 7.40 (d, 1H, J = 15.6), 7.00 (d, 2H, J = 8.4), 6.62 (br d, 2H, J = 16.2), 4.73 (s, 2H), 3.22-3.08 (m, 2H), 1.52-1.38 (m, 2H), 1.23 (br s, 18H), 0.92-0.78 (m, 3H); MS (APcI): 678.7 (100, [M+H]), 677.9 (85, [M]); calcd $C_{41}H_{48}N_3O_6$ ([M+H]) 678.9.

Example 55

3-[4-(4-(4-*tert*-Butoxycarbonylmethoxy-phenyl)-5-{4-[(E)-2-(hexadecyl-methyl-carbamoyl)-vinyl]-phenyl}-1H-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 244



244

Compound **244** was synthesized according to *General Method 8* from imidazole **60a** ($R^{1'}$ = *tert*-butyl, R^4 = 4-phenyl-(4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester))(150 mg, 0.22 mmol) in DMF (1.5 mL), with $Pd(OAc)_2$ (10 mg, 0.045 mmol), TEA (62 μL, 0.44 mmol), $(o\text{-Tolyl})_3P$ (27 mg, 0.09 mmol), and *acrylamide **61a** (70mg, 0.28 mmol) to give after purification by flash column chromatography and recrystallization *3-[4-(4-(4-tert-butoxycarbonylmethoxy-phenyl)-5-{4-[(E)-2-(hexadecyl-methyl-carbamoyl)-vinyl]-phenyl}-1H-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **244** as a yellow solid (80 mg, 50%).

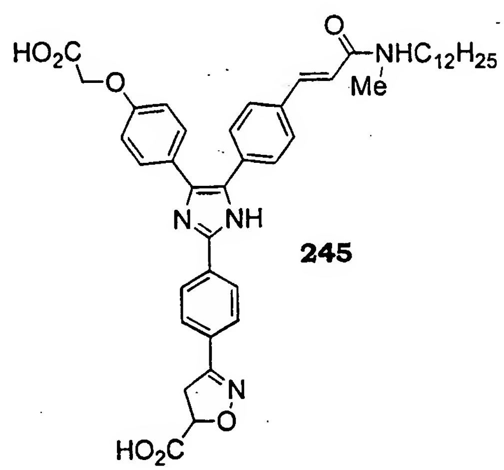
*Acrylamide **61a** was synthesized according to *General Method 9* from acryloyl chloride and dodecylamine. This precursor acrylamide **57k** (4 mmol) was then treated with methyl iodide (6mmol, 1.5 equiv.), and sodium hydride (8 mmol) in DMF (5 mL), for ~ 1 hour. The reaction was worked up, (diluted with ethyl acetate and washed with water, dried ($MgSO_4$) and concentrated *in vacuo*) and the desired acrylamide **61a** was used without further purification for the Heck reaction.

Data for *3-[4-(4-(4-tert-butoxycarbonylmethoxy-phenyl)-5-{4-[(E)-2-(hexadecyl-methyl-carbamoyl)-vinyl]-phenyl}-1H-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **244**: ^{1}H-NMR (300 MHz, $CDCl_3$):

8.40-8.15 (m, 1H), 7.85 (d, 2H, J = 7.3), 7.90-7.05 (m, 9H), 7.00 (d, 2H, J = 7.3), 5.35 (t, 1H, J = 9.5), 4.69 (s, 2H), 3.77 (d, 2H, J = 9.5), 3.70-3.40 (m, 2H), 3.30 (s, 1.5H), 3.15 (s, 1.5H), 1.85-1.60 (m, 20H), 1.60-1.30 (m, 18H), 1.15-1.00 (m, 3H).

Example 56

3-[4-(4-(4-Carboxymethoxy-phenyl)-5-{4-[(E)-2-(dodecyl-methyl-carbamoyl)-vinyl]-phenyl}-1H-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid 245



245

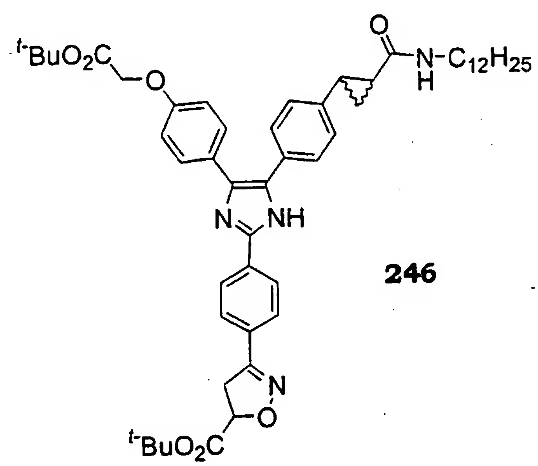
Compound **245** was synthesized according to *General Method 11* from imidazole **244** to give after recrystallization from methanol/ethyl acetate, *3-[4-(4-(4-Carboxymethoxy-phenyl)-5-{4-[(E)-2-(hexadecyl-methyl-carbamoyl)-vinyl]-phenyl}-1H-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid* **245** as a yellow solid (30 mg, 60%).

Data for *3-[4-(4-(4-Carboxymethoxy-phenyl)-5-{4-[(E)-2-(hexadecyl-methyl-carbamoyl)-vinyl]-phenyl}-1H-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid* **245**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.40-8.25 (m, 2H), 7.96 (d, 2H, *J* = 9.6), 7.90-7.50 (m, 6H), 7.63 (d, 2H, *J* = 8.7), 7.32 (br d, 1H, *J* = 14.7), 7.16 (br s, 2H), 5.29 (dd, 1H, *J* = 11.1, 6.9), 4.84 (s, 2H), 4.00-3.46 (m,

6H), 3.30 (s, 1.5H), 3.08 (s, 1.5H), 1.80-1.60 (m, 2H), 1.60-1.20 (m, 18H), 1.15-0.90 (m, 3H). MS (APcI): 735.0 (100, [M]), 735.8 (75, [M+H]); calcd $C_{43}H_{51}N_4O_7$ ([M+H]) 735.9.

Example 57

3-(4-{4-(4-*tert*-butoxycarbonylmethoxy-phenyl)-5-[4-(2-hexadecylcarbamoyl-cyclopropyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 246



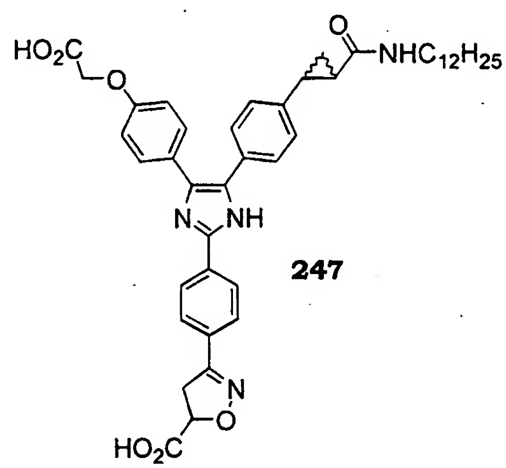
246

Imidazole **246** was synthesized from imidazole **235** (Example 46) (40 mg, 0.05 mmol) *via* treatment with bis(benzonitrile)dichloropalladium (II) (1.5 mg, 0.04 mmol) and diazomethane (excess, ~0.332 mmol). The reaction was stirred for 15 minutes, filtered through celite and concentrated *in vacuo*. Purfication *via* flash column chromatography eluting with 1% methanol in DCM gave the desired imidazole *3-(4-{4-(4-tert-butoxycarbonylmethoxy-phenyl)-5-[4-(2-hexadecylcarbamoyl-cyclopropyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **246**, 22mg (52%).

Data for *3-(4-{4-(4-tert-butoxycarbonylmethoxy-phenyl)-5-[4-(2-hexadecylcarbamoyl-cyclopropyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **246**: ^{1}H-NMR (300 MHz, $CDCl_3$ + 5% CD_3OD): 8.18-8.10 (m, 2H), 7.98-7.80 (m, 3H), 7.60-7.48 (m, 4H), 7.18-7.10 (m, 2H), 7.03-6.95 (m, 2H), 5.28-5.15 (m, 1H), 4.70-4.62 (m, 2H), 3.85-3.55 (m, 4H), 3.40-3.28 (m, 2H), 2.60-2.48 (m, 1H), 1.88-1.75 (m, 1H), 1.75-1.53 (m, 20H), 1.52-1.25 (br s, 18H), 0.83 (m, 3H).

Example 58

3-(4-{4-(4-Carboxymethoxy-phenyl)-5-[4-(2-hexadecylcarbamoyl-cyclopropyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid 247



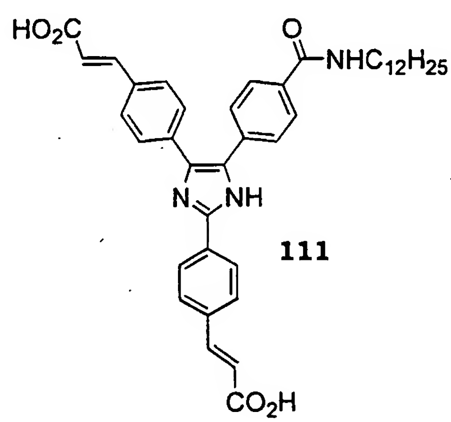
247

Compound **247** was synthesized according to *General Method 11* from imidazole **246** to give, after recrystallization from methanol/ethyl acetate, *3-(4-{4-(4-Carboxymethoxy-phenyl)-5-[4-(2-hexadecylcarbamoyl-cyclopropyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid* **247** as a yellow solid (15 mg, 78%).

Data for *3-(4-{4-(4-Carboxymethoxy-phenyl)-5-[4-(2-hexadecylcarbamoyl-cyclopropyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid* **247**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.12 (d, 2H, J = 6.3), 8.06 (t, 1H, J = 2.5), 7.79 (d, 2H, J = 6.0), 7.41 (d, 4H, J = 6.6), 7.10 (br d, 2H, J = 4.1), 6.94 (br d, 2H, J = 4.1), 5.18 (dd, 1H, J = 9.0, 5.1), 4.70 (s, 2H), 3.75 (dd, 1H, J = 12.6, 8.7), 3.61 (dd, 1H, J = 12.6, 4.8), 3.40-3.30 (m, 2H), 3.10-2.98 (m, 2H), 2.25-2.15 (m, 1H), 1.90-1.80 (m, 1H), 1.45-1.30 (m, 2H), 1.30-1.10 (br s, 18H), 0.83 (t, 3H, J = 5.1). MS (APcI): 735.3 (100, [M+H]), 647.2 (58); calcd $C_{43}H_{51}N_4O_7$ ([M+H]) 735.9.

Example 59

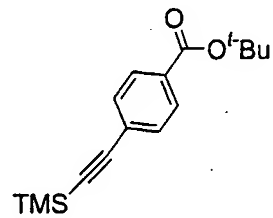
(E)-3-{4-[4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-(4-dodecylcarbamoyl-phenyl)-1*H*-imidazol-2-yl]-phenyl}-acrylic acid 111



111

4-iodobenzoic acid *tert*-butyl ester **83** (Scheme 15, R = ^{t}-Bu, 12.618 g; 41.4 mmol) was charged to a round-bottomed flask along with DMF (110 mL), trimethylsilyl- acetylene (30 mL; 207 mmol), dichlorobis(triphenylphosphine) palladium(II) (610 mg; 0.83 mmol), copper(I) iodide (95 mg; 0.41 mmol), and triethylamine (17 mL; 124 mmol). The resultant mixture was stirred at rt under N_2 for 12 h. After cooling to rt the organics were added to NH_4Cl (200 mL) and extracted with pentane (2 X 200

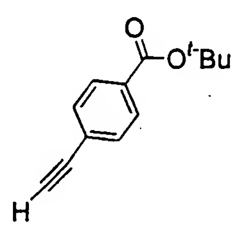
mL). The organics were then washed with water (200 mL), brine (200 mL), dried over $MgSO_4$, filtered, and concentrated to dryness. The crude material was dried *in vacuo* to provide **84** (11.4 g).



84

Data for compound **84**: ^{1}H-NMR (300 MHz, CDCl3): 7.92 (d, 2H, J = 8.1), 7.52 (d, 2H, J = 8.1), 1.61 (s, 9H), 0.23 (s, 9H).

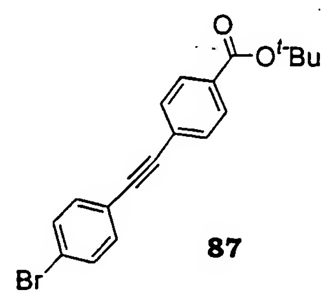
Alkyne **84** (Scheme 15, R = ^{t}-Bu, 11.4 g) was charged to a round-bottomed flask along with THF (54 mL). To this was added TBAF (1.0 M in THF, 46 mL, 45.7 mmol) and the reaction was stirred under N_2 for 1.5 h. The crude mixture was added to water (200 mL) and extracted with pentane (2 X 200 mL). Organics were then washed with brine (200 mL), dried over $MgSO_4$, filtered, and concentrated to dryness. The crude was then taken up in pentanes (200 mL) and filtered through a short pad of silica gel, concentrated, and dried *in vacuo* to provide **85** (6.7 g).



85

Data for compound **85**: ^{1}H-NMR (300 MHz, $CDCl_3$): 7.94 (d, 2H, J = 8.1), 7.52 (d, 2H, J = 8.1), 3.2 (s, 1H), 1.6 (s, 9H).

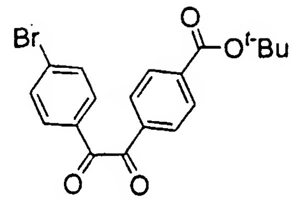
Alkyne **85** (Scheme 15, R = ^{t}-Bu, 6.7 g) was charged to a round-bottomed flask along with DMF (50 mL), 4-bromo-1-iodobenzene **86** (11.3 g, 40 mmol), copper iodide (63 mg, 0.33 mmol), dichlorobis(triphenyl-phosphine) palladium(II) (470 mg, 0.66 mmol) and triethylamine (14 mL, 100 mmol). The reaction mixture was stirred at rt under an atmosphere of nitrogen for 8 h. The crude reaction mixture was added to a mixture of hexanes/ethyl acetate (4:1, 200 mL), and washed with NH_4Cl (200 mL) and brine (200 mL), dried over $MgSO_4$, filtered, and concentrated to dryness. The crude material was dried *in vacuo* to provide a dark orange solid **87** (15.3 g). This crude was a mixture of **87** and **86**, which was not purified further.



87

Data for compound **87**: ^{1}H-NMR (300 MHz, $CDCl_3$): 7.98 (d, 2H, J = 8.0), 7.55 (d, 2H, J = 8.1), 7.51 (d, 2H, J = 8.1), 7.4 (d, 2H, J = 8.0), 1.61 (s, 9H).

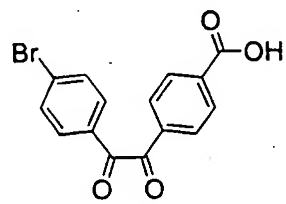
Alkyne **87** (Scheme 15, R = ^{t}-Bu, 12.0 g) was charged to a round-bottomed flask along with CCl_4 (90 mL), CH_3CN (90 mL), H_2O (135 mL), and sodium periodate (28.7 g, 134.4 mmol). After stirring for 5 min, ruthenium dioxide (100 mg, 0.74 mmol) was added and the mixture stirred at rt for 6 h. The crude was added to CH_2Cl_2 (500 mL), washed with H_2O (2 X 250 mL) and brine (250 mL), dried over $MgSO_4$, filtered, and concentrated to dryness. The crude was flashed using 10:1 hexanes/ethyl acetate to provide **88** as a white solid (10.8 g).



88

Data for compound **88**: ^{1}H-NMR (300 MHz, $CDCl_3$): 8.13 (d, 2H, J = 8.0), 8.05 (d, 2H, J = 8.1), 7.82 (d, 2H, J = 8.0), 7.64 (d, 2H, J = 8.1), 1.61 (s, 9H).

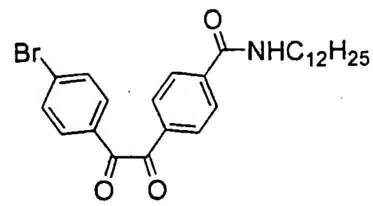
Dione **88** (Scheme 17, R = ^{t}-Bu, 1.4 g) was charged to a round-bottomed flask along with 20% TFA in CH_2Cl_2 (20 mL) and the reaction mixture was stirred for 1.5h. The crude material was concentrated and dried *in vacuo* to provide **106** (1.1 g).



106

Data for compound **106**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.15 (d, 2H, J = 8.1), 8.06 (d, 2H, J = 8.1), 7.87 (m, 4H), 1.61 (s, 9H).

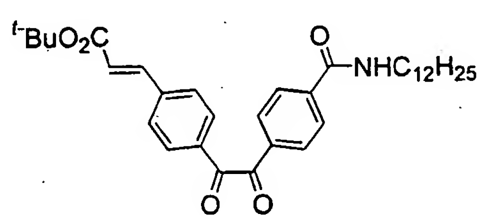
Dione **106** (Scheme 17, 300 mg) was charged to a round-bottomed flask along with dodecylamine (200 mg, 1.08 mmol), DMF (10 mL), CH_2Cl_2 (10 mL), EDCI (207 mg, 1.08 mmol), and DMAP (110 mg, 0.9 mmol), and the reaction mixture was stirred at rt for 12 h. The crude mixture was added to EtOAc (100 mL) and washed with H_2O (100 mL), and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated to dryness. The crude was then chromatographed by flash chromatography using 3:1 Hexanes/EtOAc to provide **108** (280 mg).



108

Data for Compound **108**: ^{1}H-NMR (300 MHz, $CDCl_3$): 8.02 (d, 2H, J = 8.1), 7.93 (m, 4H,), 7.87 (d, 2H, J = 8.2), 6.02 (m, 1H), 3.32 (m, 2H), 1.54 (m, 2H), 1.23 (m, 18H), 0.92 (m, 3H).

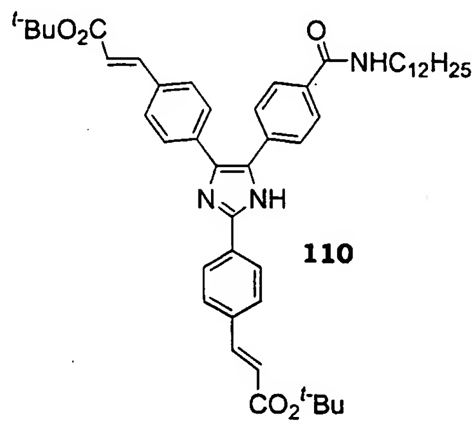
Dione **108** (Scheme 17, 200 mg) was charged to a round-bottomed flask along with t-butyl acrylate (88 μL, 60 mmol), palladium (II) acetate (2 mg, 0.01 mmol), tri-*o*-tolylphosphine (15 mg, 0.05 mmol), triethylamine (170 μL, 1.2 mmol), and DMF (10 mL), and the reaction was stirred at 100 °C under N_2 for 2h. After cooling to rt the crude was added to CH_2Cl_2 (50 mL) and washed with H_2O (50 mL), brine (50 mL), dried over $MgSO_4$, filtered, and concentrated to dryness. The compound was purified using flash chromatography with 3:1 hexanes/EtOAc as eluent to provide **109** (142 mg).



109

Data for compound **109**: ^{1}H-NMR (300 MHz, $CDCl_3$): 8.15 (d, 2H, J = 8.1), 7.95 (m, 4H,), 7.87 (d, 2H, J = 8.2), 7.62 (d, 1H, J = 15.4), 6.61 (d, 1H, J = 15.5), 5.91 (m, 1H), 3.22 (m, 2H), 1.62 (s, 9H), 1.54 (m, 2H), 1.23 (m, 18H), 0.93 (m, 3H).

I[illegible]ne **109** (Scheme 17, 130 mg) was added to a round-bottomed flask along with **34a** (55 mg, 0.24 mmol), NH_4OAc (0.55 g, 7.2 mmol), and HOAc (3 mL), and the reaction was stirred at 100 °C under N_2 for 1.5 h. After cooling to rt, the mixture was added to CH_2Cl_2 (100 mL), washed with H_2O (75 mL) and brine (75 mL), dried over $MgSO_4$, filtered, and concentrated to dryness. The crude was purified by preparative TLC (1.0 mm) using 15:1 CH_2Cl_2/MeOH to provide **110** (62 mg).



110

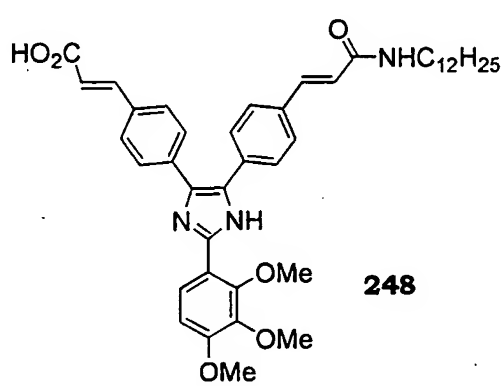
Data for imidazole **110**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.53 (m, 1H), 8.18 (d, 2H, J = 8.1), 7.95 (m, 4H,), 7.87 (d, 2H, J = 8.2), 7.61 (m, 6H), 6.65 (d, 1H, J = 15.5), 6.60 (d, 1H, J = 15.6), 3.22 (m, 2H), 1.62 (s, 9H), 1.61 (s, 9H), 1.54 (m, 2H), 1.23 (m, 18H), 0.93 (m, 3H).

Imidazole **110** (Scheme 17, 60 mg) was added to a round-bottomed flask followed by 20% TFA in CH_2Cl_2 (3.0 mL). The reaction was stirred at rt for 2.5 h. The crude mixture was concentrated to dryness and purified by preparative chromatography (1.0 mm) using (2X) 10:1 CH_2Cl_2/MeOH to provide *(E)-3-{4-[4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-(4-dodecylcarbamoyl-phenyl)-1H-imidazol-2-yl]-phenyl}-acrylic acid* **111** (24 mg).

Data for provide *(E)-3-{4-[4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-(4-dodecylcarbamoyl-phenyl)-1H-imidazol-2-yl]-phenyl}-acrylic acid* **111**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.53 (m, 1H), 8.18 (d, 2H, J = 8.1), 7.95 (m, 4H,), 7.87 (d, 2H, J = 8.2), 7.61 (m, 6H), 6.65 (d, 1H, J = 15.5), 6.60 (d, 1H, J = 15.6), 3.22 (m, 2H), 1.54 (m, 2H), 1.23 (m, 18H), 0.93 (m, 3H). MS (ESI): 648.5 (100, [M+H]); calcd $C_{41}H_{45}N_3O_5$ ([M+H]) 648.4.

Example 60

3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-(2,3,4-trimethoxy-phenyl)-1*H*-imidazol-4-yl]-phenyl}-acrylic acid 248



248

Compound **248** was synthesized according to *General Method 7* from dione **123a** (200 mg, 0.35 mmol) in acetic acid (1.5 mL), 2,3,4-

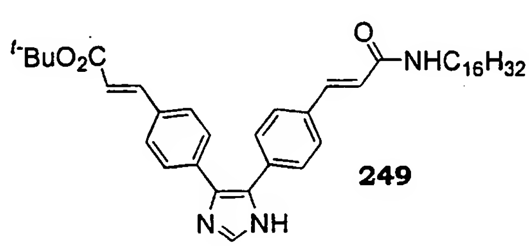
trimethoxyfbenzaldehyde (100 mg, 0.52 mmol) and NH_4OAc (809 mg, 10.5 mmol), which gives after purification by column chromatography eluting with 1-2 % methanol in DCM, 3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-(2,3,4-trimethoxy-phenyl)-1H-imidazol-4-yl]-phenyl}-acrylic acid *tert*-butyl ester. The *tert*-butyl ester was hydrolyzed according to *General Method 11* to give, after recrystallization *3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-(2,3,4-trimethoxy-phenyl)-1H-imidazol-4-yl]-phenyl}-acrylic acid* **248** as a yellow solid (204 mg, 92%).

Data for *3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-(2,3,4-trimethoxy-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid* **248**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.14 (t, 1H, J = 5.7), 7.81 (d, 2H, J = 8.7) 7.68-7.55 (m, 8H), 7.45 (d, 1H J = 15.6), 7.10 (d, 1H, J = 9.3), 6.68 (d, 1H, J = 15.9), 6.61 (d, 1H, J = 15.9), 3.94 (s ,3H), 3.92 (s, 3H), 3.85 (s, 3H), 3.16 (q, 2H, J = 6.6), 1.45 (t, 2H, J = 6.0), 1.24 (brs, 18H), 0.85 (t, 3H, J = 6.3).

LC/MS: LC: retention time 3.86 minute; MS (APcI): 694.6 (100, [M+H]), calcd $C_{42}H_{51}N_3O_6$ [M+H] 694.9.

Example 61

(E)-3-(4-{5-[4-((E)-2-Hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-acrylic acid *tert*-butyl ester 249



249

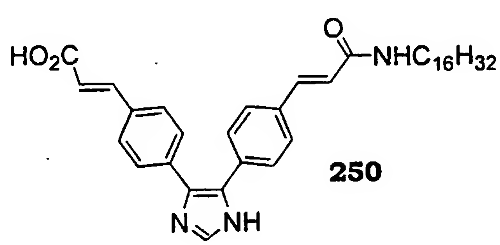
The starting dione **123b** for compound **249** was synthesized according to *General Method 15.* Imidazole **249** was synthesized from dione **123b** (1.5

g, 2.38 mmol, 1.0 eq) in acetic acid (14 mL), DMSO (4 mL), hexamethylenetetramine (1.67 g, 11.9 mmol, 5 eq) and 5.50 g, 71.4 mmol, 30 eq). The resulting imidazole was purified by flash column chromatography eluting with a gradient of 2% - 8% Methanol in DCM. The imidazole *(E)-3-(4-{5-[4-((E)-2-Hexadecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-acrylic acid tert-butyl ester* **249** was obtained as a yellow solid (1.4 g, 92%).

Data for *(E)-3-(4-{5-[4-((E)-2-Hexadecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-acrylic acid tert-butyl ester* **249**: ^{1}H NMR (400 MHz, $CDCl_3$); 7.59 (s, 1H), 7.50-7.22 (m, 10H), 6.64 (br, s, 1H), 6.38 (d, 1H, J = 15.2), 6.28 (d, 1H, J = 16.0), 3.36-3.29 (m, 2H), 1.52-1.46 (m, 2H), 1.51 (s, 9H), 1.23 (br, s, 26H), 0.86 (t, 3H, J = 6.6).

Example 62

(E)-3-(4-{5-[4-((E)-2-Hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-acrylic acid 250



250

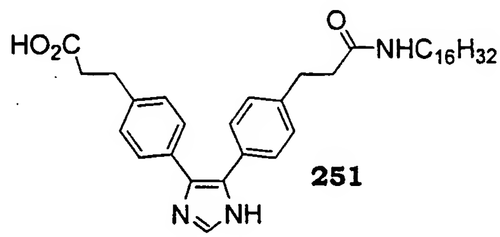
Imidazole **250** was prepared according to *General Method 11*, form imidazole **249**, to give after recrystallization from methanol/ethyl acetate, *(E)-3-(4-{5-[4-((E)-2-Hexadecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-acrylic acid* **250** as a pale yellow solid (0.77g, 60%).

Data for *(E)-3-(4-{5-[4-((E)-2-Hexadecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-acrylic acid* **250**: ^{1}H NMR (300 MHz, DMSO-d_6); 8.49 (s,

1H), 8.11 (t, 1H, J = 5.6), 7.73 (d, 2H, J = 8.1), 7.60 (d, 2H, J = 8.4), 7.59 (d, 1H, J = 15.9), 7.52 (d, 2H, J = 8.4), 7.51 (d, 2H, J = 8.1), 7.42 (d, 1H, J = 15.6), 6.62 (d, 1H, J = 15.9), 6.56 (d, 1H, J = 16.2), 3.20-3.13 (m, 2H), 1.50-1.40 (m, 2H), 1.22 (br, s, 26H), 0.84 (t, 3H, J = 6.3).

Example 63

3-(4-{5-[4-(2-Hexadecylcarbamoyl-ethyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-propionic acid 251

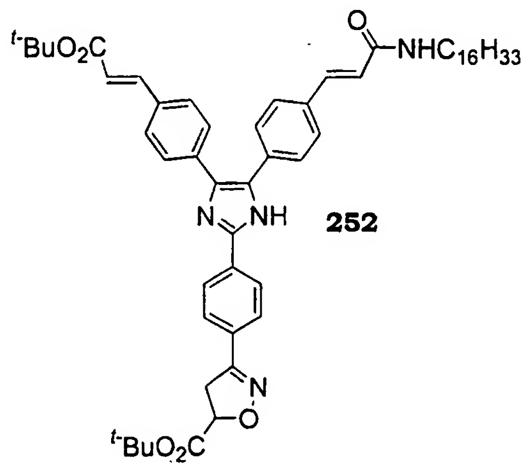


251

Imidazole **251** was obtained *via* reduction of the double bonds of imidazole **250** according to *General Method 14. 3-(4-{5-[4-(2-Hexadecylcarbamoyl-ethyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-propionic acid* **251** was obtained 15 mg (80%) after recrystallization as a white solid. Data for *3-(4-{5-[4-(2-Hexadecylcarbamoyl-ethyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-propionic acid* **251**: ^{1}H-NMR (400 MHz, CD_3OD): 8.97 (s, 1H), 8.02-7.84 (m, 1H), 7.50-7.25 (m, 8H), 3.10 (t, 2H, J = 6.2), 3.08-2.90 (m, 4H), 2.63 (t, 2H, J = 7.6), 2.51 (t, 2H, J = 7.8), 1.48-1.32 (m, 2H), 1.32-1.10 (m, 26H), 0.89 (t, 3H, J = 6.6); MS (APcI): 588.1 (100,[M]), 588.9 (96, [M+H]); calcd $C_{37}H_{53}N_3O_3$ ([M]) 587.8.

Example 64

3-(4-{4-[4-((E)-2-*tert*-Butoxycarbonyl-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 252



252

Compound **252** was synthesized according to *General Method 7* from dione **123b** (0.5 g, 0.79 mmol) in acetic acid (5.5 mL), 4-formylphenyl-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester (0.26 g, 0.95 mmol) and NH_4OAc (1.8 g, 23.8 mmol). The resulting imidazole was purified by flash column chromatography eluting with hexane/ethyl acetate (3:1). The desired *3-(4-{4-[4-((E)-2-tert-Butoxycarbonyl-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **252** was obtained as a yellow solid (0.5 g, 72 %).

Data for *3-(4-{4-[4-((E)-2-tert-Butoxycarbonyl-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **252**: ^{1}H-NMR (300 MHz, $CDCl_3$): 8.01 (br, m, 2H), 7.70-7.20 (br, m, 10H), 6.40-6.10 (br, m, 3H), 5.10 (t, 1H, J = 9.3), 3.60 (d, 2H, J = 9.3), 3.30 (br, s, 2H), 1.58 (s, 9H), 1.56 (s, 9H), 1.57 (br, s, 2H), 1.30 (br, s, 26H), 0.85 (t, 3H, J = 7.5).

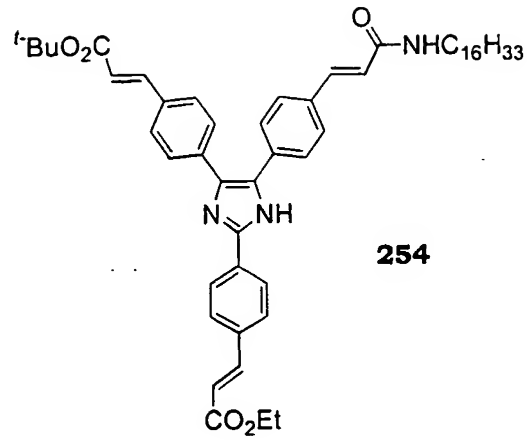
Example 65

3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid 253

Imidazole **253** was prepared according to *General Method 11*, from imidazole **252**, to give after recrystallization from methanol/ethyl acetate, *3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid* **253** as a pale yellow solid (0.3 g, 69%). Data for *3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid* **253**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.19 (d, 2H, J = 8.7), 8.10 (t, 1H, J = 5.4), 7.86 (d, 2H, J = 8.1), 7.75 (d, 2H, J = 8.4), 7.64-7.58 (m, 7H), 7.43 (d, 1H, J = 15.6), 6.65 (d, 1H, J = 15.9), 6.57 (d, 1H, J = 15.9), 5.25-5.19 (m, 1H), 3.84-3.61 (m, 2H), 3.19-3.13 (m, 2H), 1.50-1.40 (br, m, 2H), 1.22 (br, s, 25H), 0.84 (t, 3H, J = 6.60). MS (ESI): 773.8 (30, [M+H]); calcd for $C_{47}H_{56}N_4O_6$ [M+H] 773.4.

Example 66

(E)-3-(4-{2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-acrylic acid *tert*-butyl ester 254



254

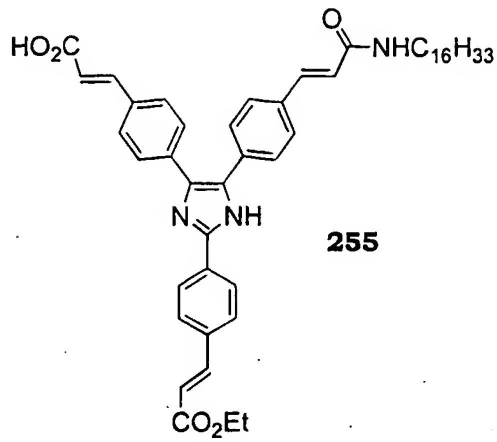
Compound **254** was synthesized according to *General Method 7* from dione **461** (1.1 g, 1.75 mmol) in acetic acid (20 mL), 4-formylcinnamic acid ethyl ester (0.53 g, 2.62 mmol) and NH_4OAc (4 g, 52 mmol). The resulting imidazole was purified by flash column chromatography eluting with DCM/methanol (95:5).

The desired imidazole *(E)-3-(4-{2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-acrylic acid tert-butyl ester* **254** was obtained as a yellow solid (1.1 g, 77 %).

Data for *(E)-3-(4-{2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-acrylic acid tert-butyl ester* **254**: ^{1}H-NMR (300 MHz, $CDCl_3$): 8.16 (d, 2H, J=7.2), 7.66 (d, 1H, J=6.4), 7.60-7.44 (br, m, 8H), 7.38 (d, 2H, J= 8.1), 7.28 (d, 2H, J =8.1), 6.41 (d, 1H, J=15.9), 6.29 (br, d, 2H, J=15.9), 6.15 (br, s, 1H), 4.27 (q, 2H, J=7.2), 3.26 (br, s, 2H), 1.53 (s, 9H), 1.46 (br, s, 2H), 1.34 (t, 3H, J= 7.2), 1.23 (br, s, 26H), 0.87 (t, 3H, J= 6.4).

Example 67

(E)-3-(4-{2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-acrylic acid 255



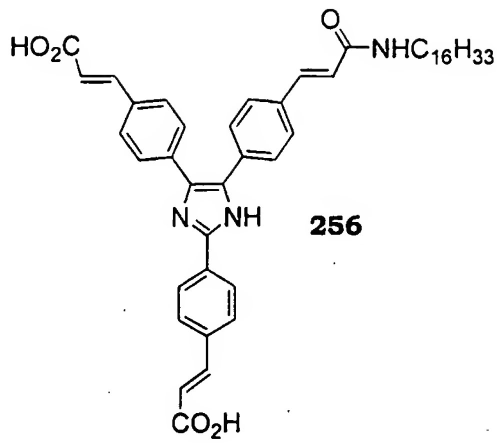
255

The *tert*-butyl ester of imidazole **254** was hydrolyzed according to *General Method 11* to give, after recrystallization, the desired imidazole *(E)-3-(4-{2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-acrylic acid* **255** as a yellow solid (0.4 g, 39 %).

Data for *(E)-3-(4-{2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-acrylic acid* **255**: ^{1}H-NMR (400 MHz, DMSO-d$_6$): 7.91 (d, 2H, J=8.0), 7.58-7.49 (m, 4H), 7.43-7.35 (m, 9H), 7.15 (t, 1H, J=6.4), 6.37 (d, 1H, J= 15.6), 6.36 (d, 1H, J=16.0), 6.29 (d, 1H, J=16.0), 4.14 (d, 2H, J=7.0), 3.23-3.16 (m, 2H), 1.48-1.38 (br, m, 2H), 1.22 (t, 3H, J= 7.0), 1.12 (br, s, 26H), 0.74 (t, 3H, J= 6.2). MS (APcI): 758.7 (100, [M+H]); calcd for $C_{48}H_{60}N_3O_5$ [M+H] 758.5.

Example 68

(E)-3-(4-{2-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-acrylic acid 256



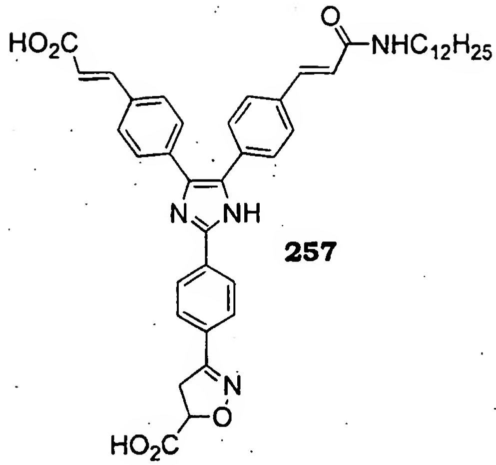
256

The ethyl ester of imidazole **255** was hydrolyzed according to *General Method 10* to give, after recrystallization, the desired imidazole *3-{4-[5-{4-[(E)-2-(3-Phenyl-propylcarbamoyl)-vinyl]-phenyl}-2-(4-pyrrolidin-1-yl-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid* **256** as a yellow solid (0.23 g, 60%).

Data for *3-{4-[5-{4-[(E)-2-(3-Phenyl-propylcarbamoyl)-vinyl]-phenyl}-2-(4-pyrrolidin-1-yl-phenyl)-1H-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid* **256**: ^{1}H-NMR (300 MHz, DMSO-d$_6$): 8.15 (d, 2H, J=8.4), 8.12 (t, 1H, J=6.0), 7.87 (d, 2H, J= 8.1), 7.75 (d, 2H, J= 8.1), 7.67-7.58 (m, 8H), 7.43 (d, 1H, J= 15.6), 6.66 (d, 1H, J=15.9), 6.64 (d, 1H, J =15.9), 6.57 (d, 1H, J=16.2), 3.45-3.20 (m, 2H), 1.50-1.40 (br, m, 2H), 1.23 (br, s, 26H), 0.84 (t, 3H, J= 6.0). MS (APcI): 730.7 (100, [M+H]); calcd for $C_{46}H_{56}N_3O_5$ [M+H] 730.4.

Example 69

3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-dodecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid 257



257

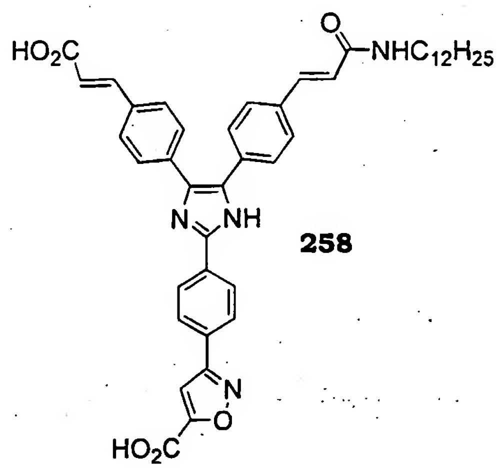
Imidazole **257** was synthesized according to *General Method 7* (Scheme 19) from dione **123a** (see *General Method 15*)(1.3 g, 2.3 mmol) in acetic acid (4.6 mL), with 3-(4-Formyl-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester (936 mg, 3.4 mmol) and NH_4OAc (5.3 g, 69 mmol), which gives, after purification *via* column chromatography eluting with DCM:methanol (95:5), 3-(4-{4-[4-((E)-2-*tert*-Butoxycarbonyl-vinyl)-phenyl]-5-[4-(2-dodecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester (1 g, 53%). The *tert*-butyl esters were hydrolyzed according to *General Method 11* to give, after recrystallization from methanol/ethyl acetate, *3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-dodecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid* **257** 200 mg (36%) as a yellow solid.

Data for *3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-dodecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid* **257**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.20 (d, 2H, J = 8.7), 8.11 (t, 1H, J = 5.1), 7.87 (d, 2H, J = 8.4), 7.76 (d, 2H, J = 8.4), 7.64-7.59 (m, 7H), 7.44 (d, 1H, J = 15.9), 6.66 (d, 1H, J = 16.2), 6.57 (d, 1H, J = 15.9), 5.22 (dd, 1H, J = 12.0, 6.9), 3.79 (dd, 1H, J = 17.1, 11.7), 3.65 (dd, 1H, J

= 17.4, 7.2), 3.17 (q, 2H, J = 6.6), 1.45 (t, 2H, J = 6.3), 1.24 (s, 18H), 0.85 (t, 3H, J = 6.6). LC/MS: LC: retention time 3.60 minute; MS (APcI): 717.7 (50, [M+H]), 645.6 (100, [M+H-CH_2CHCO_2H]), calcd $C_{43}H_{48}N_4O_6$ [M+H] 717.9.

Example 70

3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-dodecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-isoxazole-5-carboxylic acid 258



258

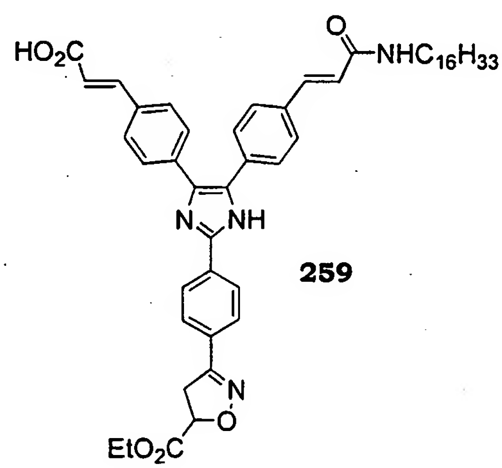
Imidazole **258** was synthesized according to *General Method 7* (Scheme 19) from dione **123a** (see *General Method 15*) (300 mg, 0.52 mmol) in acetic acid (2 mL), with 3-(4-Formyl-phenyl)-isoxazole-5-carboxylic acid ethyl ester **37** (synthesized according to *General Method 1* using the appropriate alkyne) (192 mg, 0.78 mmol) and NH_4OAc (1.2 g, 15.6 mmol), which gives, after purification *via* column chromatography eluting with DCM:methanol (95:5), *3-(4-{4-[4-((E)-2- tert-Butoxycarbonyl - vinyl)-phenyl]-5-[4-(2-dodecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-isoxazole-5-carboxylic acid ethyl ester* (200 mg, 48%). The *tert*-butyl and ethyl esters are hydrolyzed according to *General Method 10* to

give, after recrystallization from methanol/ethyl acetate, *3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-dodecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-isoxazole-5-carboxylic acid* **258** 35 mg (55%) as a yellow solid.

Data for *3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-dodecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-isoxazole-5-carboxylic acid* **258**: ^{1}H-NMR (300 MHz, DMSO-d$_6$): 8.24 (d, 2H, J = 8.4), 8.14 (t, 1H, J = 4.5), 8.08 (d, 2H, J = 8.4), 7.83 (s, 1H), 7.72 (d, 2H, J = 8.1), 7.63-7.59 (m, 7H), 7.42 (d, 1H, J = 15.6), 6.64 (d, 1H, J = 15.6), 6.54 (d, 1H, J = 15.9), 3.15 (t, 2H, J = 4.5), 1.44 (t, 2H, J = 5.7), 1.23 (s, 18H), 0.83 (t, 3H, J = 6.3). LC/MS: LC: retention time 3.72 minute; MS (APcI): 715.1 (100, [M+H]), calcd $C_{43}H_{46}N_4O_6$ [M+H] 715.9.

Example 71

3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester 259



259

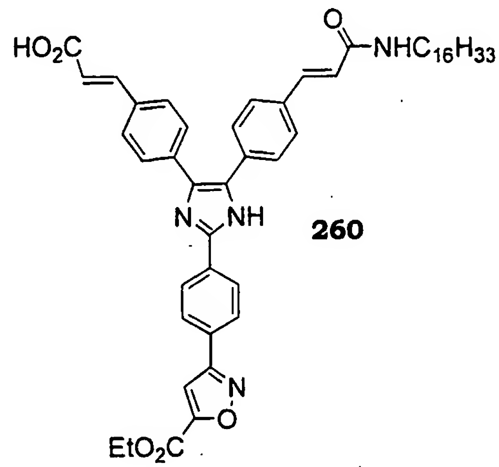
Imidazole **259** was synthesized according to *General Method 7* (Scheme 19) from dione **123b** (520 mg, 0.83 mmol) in acetic acid (2 mL), with 3-

(4-formyl-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (306 mg, 1.2 mmol) and NH_4OAc (1.9 g, 25 mmol), which gives, after purification *via* column chromatography eluting with DCM:methanol (95:5), 3-(4-{4-[4-((E)-2-*tert*-Butoxycarbonyl-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (300 mg). The *tert*-butyl ester was hydrolyzed according to *General Method 11* to give, after recrystallization from methanol/ethyl acetate, *3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester* **259,** 200 mg (72%) as a yellow solid.

Data for *3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester* **259**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.19 (d, 2H, J = 8.4), 8.10 (t, 1H, J = 5.1), 7.85 (d, 2H, J = 8.4), 7.74 (d, 2H, J = 8.1), 7.63-7.60 (m, 7H), 7.43 (d, 1H, J = 15.6), 6.65 (d, 1H, J = 15.9), 6.56 (d, 1H, J = 16.2), 5.31(dd, 1H, J = 11.7, 6.9), 4.19 (q, 2H, J = 7.2), 3.80 (dd, 1H, J = 17.7, 12.0), 3.68 (dd, 1H, J = 17.1, 6.6), 3.17 (q, 2H, J = 5.4), 1.45 (t, 2H, J = 5.7), 1.27-1.23 (m, 29H), 0.85 (t, 3H, J = 5.4). LC/MS: LC: retention time 4.33 minute; MS (APcI): 801.1 (100, [M+H]), calcd $C_{49}H_{60}N_4O_6$ [M+H] 801.0.

Example 72

3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-isoxazole-5-carboxylic acid ethyl ester 260



260

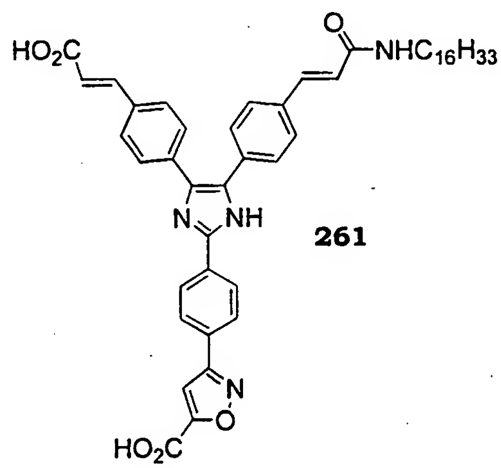
Imidazole **260** was synthesized according to *General Method 7* (Scheme 19) from dione **123b** (see *General Method 15*) (500 mg, 0.79 mmol) in acetic acid (4 mL), with 3-(4-Formyl-phenyl) -isoxazole-5-carboxylic acid ethyl ester (292 mg, 1.2 mmol) and NH_4OAc (1.8 g, 24 mmol), which gives after purification *via* column chromatography eluting with DCM:methanol (95:5), 3-(4-{4-[4-((E)-2-*tert*-Butoxycarbonyl -vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-isoxazole-5-carboxylic acid ethyl ester (377 mg, 56%). The *tert*-butyl ester was hydrolyzed according to *General Method 11* to give, after recrystallization from methanol/ethyl acetate, *3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-isoxazole-5-carboxylic acid ethyl ester* **260,** 403 mg (100%) as a yellow solid.

Data for *3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-isoxazole-5-*

carboxylic acid ethyl ester **260**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.29 (d, 2H, J = 8.4), 8.20 (d, 2H, J = 7.8), 8.12 (t, 1H, J = 5.4), 8.03 (s, 1H), 7.78 (d, 2H, J = 7.8), 7.66-7.59 (m, 7H), 7.44 (d, 1H, J = 15.9), 6.67 (d, 1H, J = 15.6), 6.59 (d, 1H, J = 16.2), 4.12 (q, 2H, J = 7.2), 3.17 (q, 2H, J = 6.0), 1.45 (t, 2H, J = 6.0), 1.36 (t, 3H, J = 7.2), 1.23 (s, 26H), 0.84 (t, 3H, J = 6.6). LC/MS: LC: retention time 4.44 minute; MS (APcI): 799 (100, [M+H]), calcd $C_{49}H_{58}N_4O_6$ [M+H] 800.

Example 73

3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-isoxazole-5-carboxylic acid 261



261

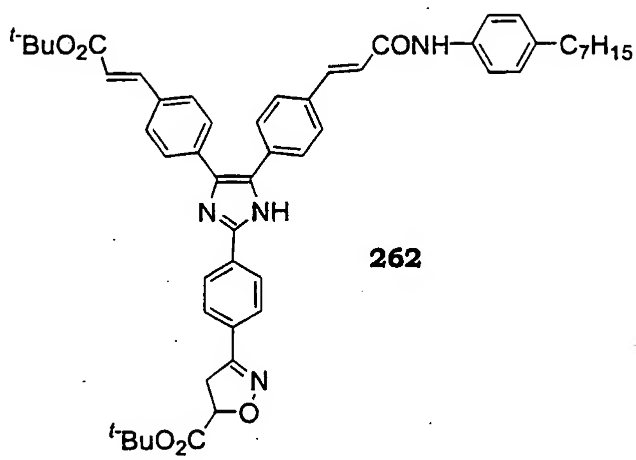
Imidazole **261** was synthesized from imidazole **260** according to *General Method 10* to give, after recrystallization from methanol/ethyl acetate, *3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-isoxazole-5-carboxylic acid* **261**, 217 mg (75%) as a yellow solid.

Data for *3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-isoxazole-5-*

carboxylic acid **261**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.31 (d, 2H, J = 8.1), 8.19 (d, 2H, J = 8.4), 8.12 (t, 1H, J = 5.1), 7.92 (s, 1H), 7.78 (d, 2H, J = 8.1), 7.66-7.59 (m, 7H), 7.44 (d, 1H, J = 15.9), 6.67 (d, 1H, J = 15.6), 6.59 (d, 1H, J = 15.9), 3.16 (q, 2H, J = 6.0), 1.45 (t, 2H, J = 6.0), 1.23 (s, 26H), 0.84 (t, 3H, J = 5.7). LC/MS: LC: retention time 4.18 minute; MS (APcI): 771 (100, [M+H]), calcd $C_{47}H_{54}N_4O_6$ [M+H] 772.

Example 74

3-[4-(4-[4-((E)-2-*tert*-Butoxycarbonyl-vinyl)-phenyl]-5-{4-[2-(4-heptyl-phenylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 262



262

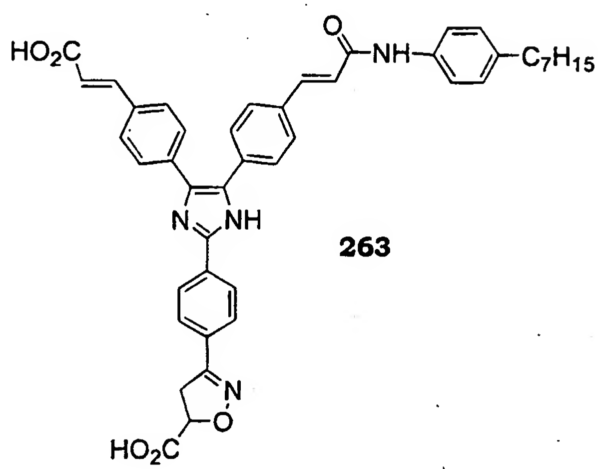
Imidazole **262** was synthesized according to *General Method 7* (Scheme 19) from dione **123c** (see *General Method 15*) (285 mg, 0.49 mmol) in acetic acid (3 mL), with 3-(4-Formyl-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester (162 mg, 0.59 mmol) and NH_4OAc (758 mg, 9.9 mmol), which gives after purification *via* column chromatography eluting with DCM:methanol (95:5), *3-[4-(4-[4-((E)-2-tert-Butoxycarbonyl-vinyl)-phenyl]-5-{4-[2-(4-heptyl-phenylcarbamoyl)-vinyl]-*

phenyl}-1H-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester **262** (400 mg, 98%).

Data for *3-[4-(4-[4-((E)-2-tert-Butoxycarbonyl-vinyl)-phenyl]-5-{4-[2-(4-heptyl-phenylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **262**: ^{1}H-NMR (300 MHz, $CDCl_3$): 8.00 (d, 2H, J = 6.3), 7.64-7.42 (m, 8H), 7.42-7.28 (m, 4H), 7.28-7.15 (brs, 2H), 7.09 (d, 2H, J = 7.8), 6.84 (d, 1H, J = 15.6), 6.56 (d, 1H, J = 16.2), 5.06 (t, 1H, J = 10.7), 3.60-3.45 (m, 2H), 2.55 (t, 2H, J=7.4), 1.65-1.40 (m, 20H), 1.40-1.15 (m, 8H), 0.88 (t, 3H, J=5.9).

Example 75

3-[4-(4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-{4-[2-(4-heptyl-phenylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid 263



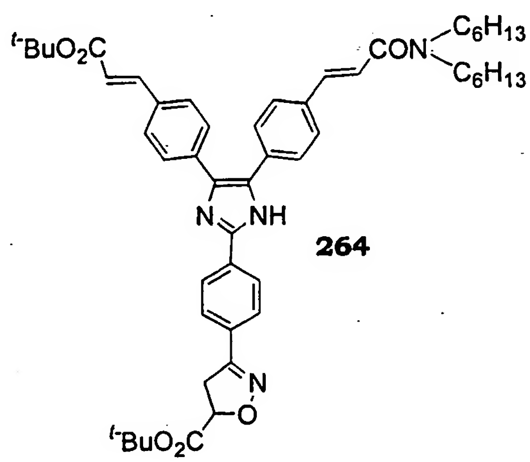
263

Imidazole **263** was synthesized from imidazole **262** according to *General Method 11* to give, after recrystallization from methanol/ethyl acetate, *3-[4-(4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-{4-[2-(4-heptyl-phenylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid* **263**, 200 mg (64%) as a yellow solid.

Data for *3-[4-(4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-{4-[2-(4-heptyl-phenylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid* **263**: ^{1}H-NMR (300 MHz, DMSO-d_6): 10.16 (s, 1H), 8.19 (d, 2H, J = 8.4), 7.87 (d, 2H, J = 8.4), 7.76 (d, 2H, J = 7.8), 7.65-7.52 (m, 10H), 7.14 (d, 2H, J = 8.7), 6.84 (d, 1H, J = 15.6), 6.56 (d, 1H, J = 15.9), 5.22 (dd, 1H, J = 11.7, 6.9), 3.90-3.55 (m, 2H), 2.4-2.6 (m, 2H) 1.6-1.45 (m, 2H), 1.65-1.10 (m, 8H), 0.85 (t, 3H, J = 6.6). MS (APcI): 723.6 (48, [M+H]), 651.8 (82), 635.6 (100); calcd $C_{44}H_{43}N_4O_6$ ([M+H]) 723.4.

Example 76

3-(4-{4-[4-((E)-2-*tert*-Butoxycarbonyl-vinyl)-phenyl]-5-[4-(2-dihexylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 264



264

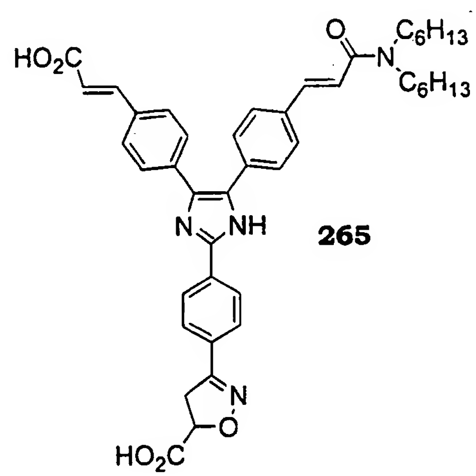
Imidazole **264** was synthesized according to *General Method 7* (Scheme 19) from dione **123d** (see *General Method 15*) (731 mg, 1.28 mmol) in acetic acid (4 mL), with 3-(4-Formyl-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester (422 mg, 1.54 mmol) and NH_4OAc (1.97 g, 26 mmol), which gives after purification *via* column

chromatography eluting with DCM:methanol (95:5), *3-(4-{4-[4-((E)-2-tert-Butoxycarbonyl-vinyl)-phenyl]-5-[4-(2-dihexylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **264** (526 mg, 53%).

Data for *3-(4-{4-[4-((E)-2-tert-Butoxycarbonyl-vinyl)-phenyl]-5-[4-(2-dihexylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **264**: ^{1}H-NMR (300 MHz, $CDCl_3$): 8.23 (d, 2H, J = 8.7), 7.69 (d, 2H, J = 8.7), 7.60-7.36 (m, 8H), 7.32 (d, 2H, J = 8.4), 6.71 (d, 1H, J = 15.3), 6.29 (d, 1H, J = 15.9), 5.08 (t, 1H, J = 9.3), 3.56 (d, 1H, J = 10.2), 3.45-3.30 (m, 4H), 1.60-1.40 (m, 22H), 1.40-1.17 (m, 12H), 0.96-0.80 (m, 6H).

Example 77

3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-dihexylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid 265



265

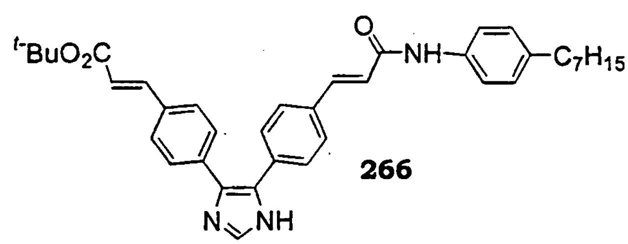
Imidazole **265** was synthesized from imidazole **264** according to *General Method 11* to give, after recrystallization from methanol/ethyl acetate, *3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-dihexylcarbamoyl-vinyl)-*

phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid **265**, 300 mg (62%) as a yellow solid.

Data for *3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-dihexylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid* **265**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.19 (d, 2H, J = 8.7), 7.85 (d, 2H, J = 8.4), 7.76 (d, 2H, J = 8.7), 7.74 (d, 2H, J = 8.1), 7.68-7.55 (m, 5H), 7.50 (d, 1H, J = 15.0), 7.14 (d, 1H, J = 15.6), 6.56 (d, 1H, J = 16.2), 5.21 (dd, 1H, J = 11.4, 6.9), 3.78 (dd, 1H, J = 17.1, 11.7), 3.64 (dd, 1H, J = 17.4, 6.9), 3.46 (t, 2H, J = 6.4), 3.23 (t, 2H, J = 7.4), 1.6-1.4 (m, 4H), 1.4-1.15 (m, 12H), 0.95-0.75 (m, 6H). MS (APcI): 717.2 (55, [M+H]), 215.3 (100); calcd $C_{43}H_{49}N_4O_6$ ([M+H]) 717.5.

Example 78

(E)-3-[4-(5-{4-[(E)-2-(4-Heptyl-phenylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenyl]-acrylic acid *tert*-butyl ester 266



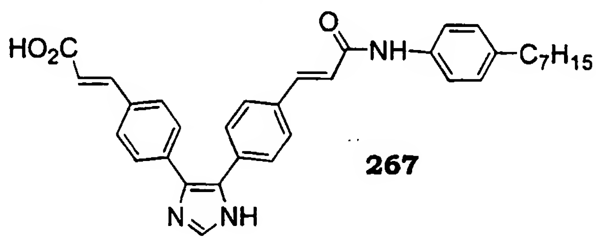
266

Imidazole **266** was synthesized according to *General Method 7* (Scheme 19) from dione **123c** (see *General Method 15*) (300 mg, 0.52 mmol) in acetic acid (6 mL), with hexamethylene tetramine (360 mg, 2.58 mmol) and NH_4OAc (1.19 g, 15.5 mmol), which gives after purification *via* column chromatography eluting with DCM:methanol (95:5), *(E)-3-[4-(5-{4-[(E)-2-(4-Heptyl-phenylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenyl]-acrylic acid tert-butyl ester* **266** (110 mg, 36%).

Data for *(E)-3-[4-(5-{4-[(E)-2-(4-Heptyl-phenylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenyl]-acrylic acid tert-butyl ester* **266**: [1]H-NMR (300 MHz, $CDCl_3$): 8.96 (br, s, 1H), 7.77 (br, s, 1H), 7.61 (d, 2H, J = 7.8), 7.61-7.20 (m, 10H), 7.09 (d, 2H, J = 8.0), 6.67 (d, 1H, J = 15.3), 6.27 (d, 1H, J = 15.9), 2.54 (br, t, 2H, J = 7.2), 1.60-1.48 (m, 2H), 1.51 (s, 9H), 1.34-1.20 (m, 8H), 0.87 (t, 3H, J = 6.6).

Example 79

(E)-3-[4-(5-{4-[(E)-2-(4-Heptyl-phenylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenyl]-acrylic acid 267



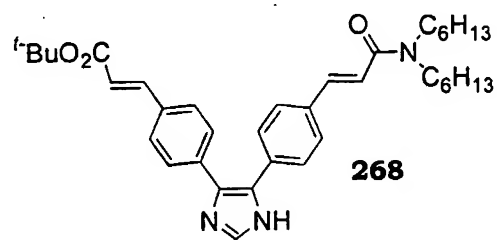
267

Imidazole **267** was synthesized from imidazole **266** according to *General Method 11* to give, after recrystallization from methanol/ethyl acetate, *(E)-3-[4-(5-{4-[(E)-2-(4-Heptyl-phenylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenyl]-acrylic acid* **267**, 31 mg (28%) as a yellow solid.

Data for *(E)-3-[4-(5-{4-[(E)-2-(4-Heptyl-phenylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenyl]-acrylic acid* **267**: [1]H-NMR (400 MHz, DMSO-d_6): 12.40 (br, s, 1H), 10.12 (s, 1H), 7.95 (s, 1H), 7.69 (d, 2H, J = 8.0), 7.63-7.51 (m, 10H), 7.14 (d, 2H, J = 8.4), 6.82 (d, 1H, J = 16.0), 6.53 (d, 1H, J = 16.0), 2.52 (t, 2H, J =8.0), 1.58-1.50 (br, m, 2H), 1.30-1.22 (br, m, 8H), 0.85 (t, 3H, J =6.8). MS (APcI): 534.4 (100, [M+H]); calcd for $C_{34}H_{36}N_3O_3$ [M+H] 534.3.

Example 80

(E)-3-(4-{5-[4-((E)-2-Dihexylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-acrylic acid *tert*-butyl ester 268



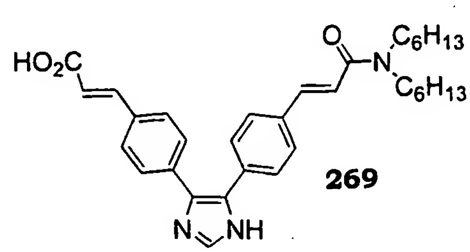
268

Imidazole **268** was synthesized according to *General Method 7* (Scheme 19) from dione **123d** (see *General Method 15*) (410 mg, 0.71 mmol) in acetic acid (5 mL), with hexamethylenetetramine (1.05 g, 21.4 mmol) and NH_4OAc (1.97 g, 26 mmol), which gives after purification *via* column chromatography eluting with DCM:methanol (95:5), *(E)-3-(4-{5-[4-((E)-2-Dihexylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-acrylic acid tert-butyl ester* **268** (280 mg, 68%).

Data for *(E)-3-(4-{5-[4-((E)-2-Dihexylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-acrylic acid tert-butyl ester* **268**: ^{1}H-NMR (400 MHz, $CDCl_3$): 8.06 (s, 1H), 7.56-7.50 (m, 6H), 7.45 (d, 2H, J = 8.0), 7.42 (d, 2H, J = 8.0), 6.82 (d, 1H, J = 16.0), 6.34 (d, 1H, J = 16), 3.34-3.36 (m, 4H), 1.66-1.56 (m, 4H), 1.62 (s, 9H), 1.32 (br, s, 12H), 0.87 (t, 6H, J = 6.8).

Example 81

(E)-3-(4-{5-[4-((E)-2-Dihexylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-acrylic acid 269



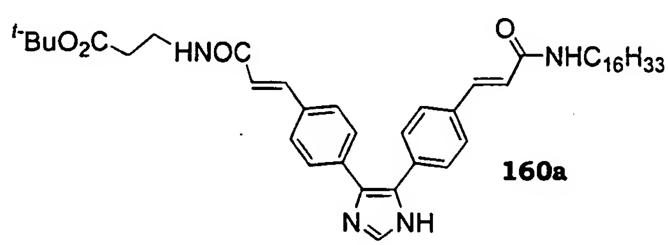
269

Imidazole **269** was synthesized from imidazole **268** according to *General Method 11* to give, after recrystallization from methanol/ethyl acetate, *(E)-3-(4-{5-[4-((E)-2-Dihexylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-acrylic acid* **269**, 50 mg (18 %) as a yellow solid.

Data for *(E)-3-(4-{5-[4-((E)-2-Dihexylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-acrylic acid* **269**: ^{1}H-NMR (300 MHz, DMSO-d_6): 7.86 (s, 1H), 7.68 (br, d, 4H, J = 6.3), 7.61-7.44 (m, 6H), 7.11 (d, 1H, J = 15.0), 6.52 (d, 1H, J = 15.9), 3.45 (t, 4H, J = 7.2), 1.51 (br, m, 4H), 1.27 (br, s, 12H), 0.86 (t, 6H, J =7.5). MS (APcI): 528.5 (100, [M+H]); mass calcd for $C_{33}H_{42}N_3O_3$ [M+H] 528.3.

Example 82

3-[3-(4-{5-[4-((E)-2-Hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-allanoylamino]-propionic acid 160a



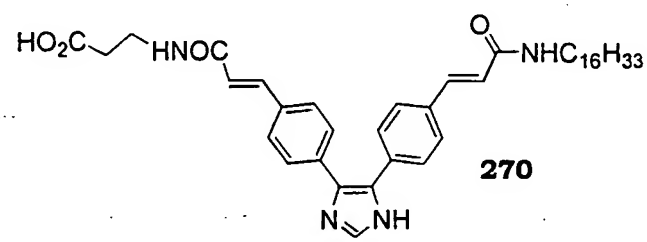
160a

Compound **160a** was synthesized according to *General Method 6*, from imidazole **250** (0.41 g, 0.7 mmol) in $CHCl_3$ (5 mL) and DMF (5 mL), EDCI (0.16 g, 0.84 mmol), DMAP (0.086 g, 0.7 mmol), H-β-ALA-O^{t}Bu .HCl (0.15 g, 0.84 mmol). After purification *via* column chromatography eluting with ethyl acetate:hexane the imidazole precursor *3-[3-(4-{5-[4-((E)-2-Hexadecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-allanoylamino]-propionic acid tert-butyl ester* **160a** (0.2 g, 40%). (Scheme 25)

Data for *3-[3-(4-{5-[4-((E)-2-Hexadecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-allanoylamino]-propionic acid tert-butyl ester* **160a**: ^{1}H-NMR (400 MHz, $CDCl_3$): 8.06 (s, 1H), 7.56-7.50 (m, 6H), 7.45 (d, 2H, J = 8.0), 7.42 (d, 2H, J = 8.0), 6.82 (d, 1H, J = 16.0), 6.34 (d, 1H, J = 16), 3.34-3.36 (m, 4H), 1.66-1.56 (m, 4H), 1.62 (s, 9H), 1.32 (br, s, 12H), 0.87 (t, 6H, J = 6.8).

Example 83

3-[3-(4-{5-[4-((E)-2-Hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-allanoylamino]-propionic acid 270



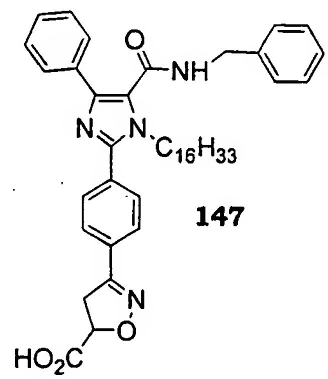
270

Imidazole **270** was synthesized from imidazole **160a** according to *General Method 11* to give, after recrystallization from methanol/ethyl acetate, *3-[3-(4-{5-[4-((E)-2-Hexadecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-allanoylamino]-propionic acid* **270**, 62 mg (30%) as a yellow solid.

Data for *3-[3-(4-{5-[4-((E)-2-Hexadecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-allanoylamino]-propionic acid* **270**: ^{1}H-NMR (300 MHz, DMSO-d_6): 12.22 (br, s, 1H), 8.18 (t, 1H, J = 6.5), 8.06 (t, 1H, J = 6.6), 7.91 (s, 1H), 7.56-7.49 (m, 8H), 7.41 (d, 1H, J = 15.9), 7.39 (d, 1H, J = 15.3), 6.63 (d, 1H, J = 16.0), 6.60 (d, 1H, J =15.9), 3.44-3.24 (m, 2H), 3.19-3.12 (br, m, 2H), 2.45 (t, 2H, J =6.3), 1.48-1.40 (m, 2H), 1.23 (br, s, 26H), 0.84 (t, 3H, J = 7.5). MS (APcI): 655.7 (100, [M+H]); calcd $C_{40}H_{55}N_4O_4$ [M+H] 655.4.

Example 84

3-[4-(5-Benzylcarbamoyl-1-hexadecyl-4-phenyl-1*H*-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid 147



147

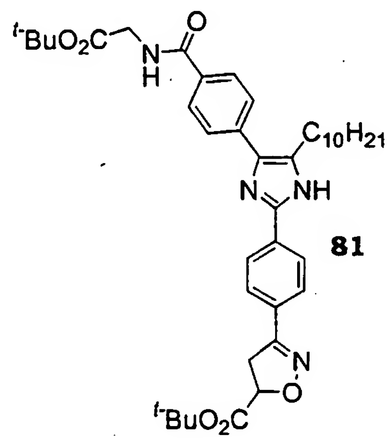
Carboxylic acid **142** (300 mg, 1.03 mmol), amine **143** (248 mg, 1.03 mmol), isocyanide **144** (120 mg, 1.03 mmol), and phenylglyoxal **145** (138 mg, 1.03 mmol) were added to a round-bottomed flask along with a 1:1 mixture of THF/MeOH (10 mL) and the mixture was stirred at rt for 4 days. The reaction mixture was concentrated and dried *in vacuo* to provide crude Ugi product **146** which was added to AcOH (10 mL) and NH_4OAc (2.3 g , 30.9 mmol) and heated to 100 °C for 1.5 h. After cooling the reaction mixture was added to CH_2Cl_2 (100 mL) and washed with H_2O (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated to dryness. Purification by flash column chromatography using 2:1 Hexanes/EtOAc provided the precursor ester **146a** (322 mg).

The ester of **146a** (320 mg, 0.43 mmol) was then added to a round-bottomed flask along with 20% TFA in CH_2Cl_2 (5 mL) and stirred at rt for 1.5 h. The reaction was concentrated and dried *in vacuo* to provide *3-[4-(5-Benzylcarbamoyl-1-hexadecyl-4-phenyl-1H-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid* **147** (288 mg).

Data for *3-[4-(5-Benzylcarbamoyl-1-hexadecyl-4-phenyl-1H-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid* **147**: ^{1}H-NMR (300 MHz, $CDCl_3$): 7.65 (m, 4H), 7.59 (m, 2H), 7.32 (m, 6H), 7.18 (m, 2H), 6.20 (m, 1H), 5.08 (m, 1H), 4.44 (m, 2H), 4.38 (m, 2H), 3.54 (m, 1H), 3.21 (m, 1H), 1.62 (m, 2H), 1.20 (m, 26H), 0.82 (m, 3H). MS (ESI): 691.6 (100, [M+H]); calcd $C_{43}H_{55}N_4O_4$ ([M+H]) 691.45.

Example 85

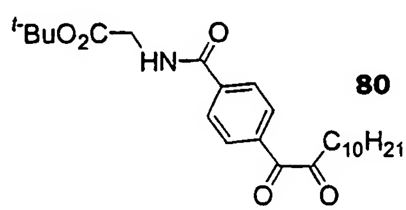
3-{4-{4-[4-(*tert*-Butoxycarbonylmethyl-carbamoyl)-phenyl]-5-decyl-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester 81



81

4-Iodo-benzoic acid **74** (4.77 mmol), was dissolved in DCM (30mL) and the mixture cooled to 0 °C. Oxalyl chloride (9.54 mmol) was added followed by 1 drop of DMF. The mixture was stirred for 30 mins at 0 °C then allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was *concentrated in vacuo*. The residue was resuspended in DCM (30 mL). Glycine *tert*-butyl ester **76** (5.72 mol) was added, and the reaction mixture allowed to stir overnight. The reaction mixture was then washed with 1N HCl aq. (2 x 10 mL), sat. sodium bicarbonate aq. (2 x 10 mL), brine (10 mL), dried ($MgSO_4$) and

concentrated *in vacuo*. The crude residue **77** was used for the next step. Iodide **77** (6.6 mmol), was dissolved in dry THF (26 mL), 1-dodecyne (1.48 mL, 6.9mmol), $PdCl_2(PPh_3)_2$ (230 mg), CuI (16mg), and triphenyl phosphine (43 mg), and triethylamine (1.85 mL) was added. The reaction mixture was stirred for 3 hours at room temperature. Then diluted with sat. ammonium chloride aq. and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with 1N HCl aq. (2 x 10 mL), sat. sodium bicarbonate aq. (2 x 10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Alkyne **79**, 2g (72 %) was obtained after purification *via* column chromatography eluting with ethyl acetate:hexane (20:80). This alkyne was then oxidized. Alkyne **79** (1.2g, 3 mmol) was dissolved in $CHCl_3$:CH_3CN:H_2O (18mL:18mL:27mL). RuO_2 (8 mg, 0.06 mmol) was added followed by sodium periodate (2.56g, 12 mmol). The reaction mixture was allowed to stir for 18 hours. Dione **80** 675mg (52 %) was obtained after purification *via* column chromatography eluting with ethyl acetate:hexane (1:9), as a white foam (Scheme 14).



80

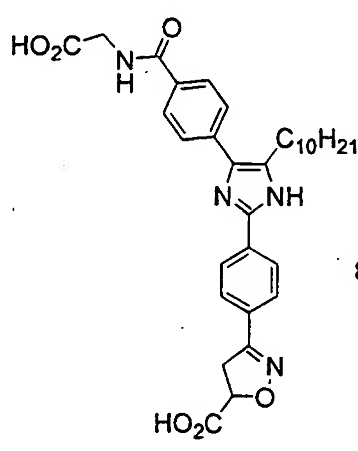
Data for Dione **80**: ^{1}H-NMR (300 MHz, $CDCl_3$): 8.05 (d, 2H, J = 8.7), 7.91 (d, 2H, J = 8.7), 6.80 (br s, 1H), 4.15 (d, 2H, J = 4.8), 2.89 (t, 2H, J = 7.4), 1.78-1.60 (m, 2H), 1.51 (br s, 9H), 1.42-1.10 (m, 14H), 0.88 (t, 3H, J = 6.5); MS (APcI): 417.3 (100, [M-CH_3+H]), 432.3 (8, [M+H]), 376.3 (48); calcd $C_{25}H_{37}NO_5$ ([M+H]) 432.6.

Imidazole **81** was synthesized according to *General Method 7* (Scheme 19) from dione **80** (336 mg, 0.78 mmol) in acetic acid (5 mL), with 3-(4-formyl-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester (214 mg, 0.78 mmol) and NH_4OAc (1.8 g, 23 mmol), which gives after purification *via* column chromatography eluting with DCM:methanol (95:5), *3-(4-{4-[4-(tert-Butoxycarbonylmethyl-carbamoyl)-phenyl]-5-decyl-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **81**, 180 mg (34%).

Date for *3-(4-{4-[4-(tert-Butoxycarbonylmethyl-carbamoyl)-phenyl]-5-decyl-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid tert-butyl ester* **81**: ^{1}H-NMR (300 MHz, $CDCl_3$): 7.96 (d, 2H, J = 8.1), 7.75 (d, 2H, J = 8.1), 7.63 (d, 2H, J = 7.2), 7.57 (d, 2H, J = 8.1), 6.98-6.86 (m, 1H), 5.03 (dd, 1H, J = 9.9, 8.1), 4.11 (d, 2H, J = 5.1), 3.65-3.45 (m, 2H), 2.75 (t, 2H, J = 7.5), 1.72-1.60 (m, 2H), 1.49 (br s, 18H), 1.40-1.05 (m, 14H), 0.84 (t, 3H, J = 6.6); MS (APcI): 687.3 (100, [M+H]); calcd $C_{40}H_{54}N_4O_6$ ([M+H]) 687.4.

Example 86

3-(4-{4-[4-(Carboxymethyl-carbamoyl)-phenyl]-5-decyl-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid 82



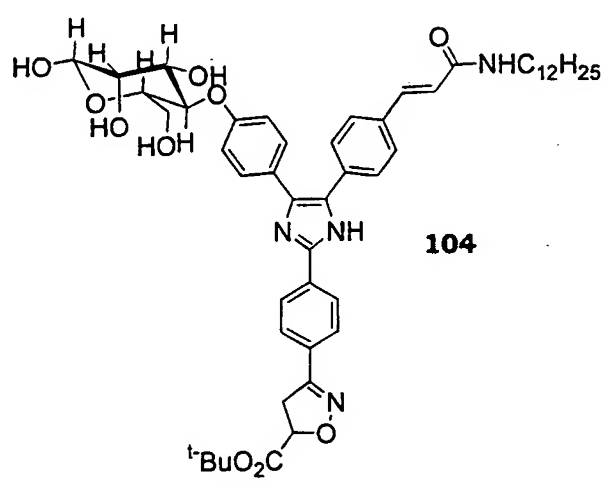
82

Imidazole **82** was synthesized from imidazole **81** according to *General Method 11* to give, after recrystallization from methanol/ethyl acetate, *3-(4-{4-[4-(Carboxymethyl-carbamoyl)-phenyl]-5-decyl-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid* **82**, 119 mg (91%) as a pale yellow solid.

Data for *3-(4-{4-[4-(Carboxymethyl-carbamoyl)-phenyl]-5-decyl-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid* **82**:
^{1}H-NMR (400 MHz, CD_3OD): 7.99 (d, 2H, J = 8.0), 7.98 (d, 2H, J = 7.6), 7.76 (d, 2H, J = 8.4), 7.74 (d, 2H, J = 8.0), 5.16 (dd, 1H, J = 12.0, 7.2), 4.12 (s, 2H), 3.72 (dd, 1H, J = 17.2, 12.0), 3.59 (dd, 1H, J = 17.2, 6.8), 2.88 (t, 2H, J = 7.6), 1.80-1.68 (m, 2H), 1.42-1.15 (m, 14H), 0.87 (t, 3H, J = 6.8); MS (APcI): 575.3 (100, [M+H]), 487.4 (95); calcd $C_{32}H_{39}N_4O_6$ ([M+H]) 575.7.

Example 87

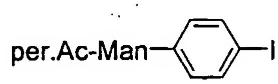
Compound **104**



104

4-Iodophenol **96** (Scheme 16, 3.38 g; 15.4 mmol) was charged to a round-bottomed flask along with D-mannose pentaacetate (5.0 g, 12.8 mmol), and CH_2Cl_2 (20 mL) followed by slow addition of $BF_3.OEt_2$ (8mL, 64.0

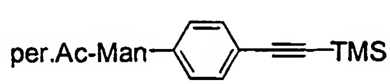
mmol). After the addition was complete the reaction stirred at rt under N_2 for 8 h. The crude reaction mixture was added to CH_2Cl_2 (200 mL) and washed with H_2O (200 mL) and brine (200 mL), dried over $MgSO_4$, filtered, and concentrated to dryness. Purification by flash column chromatography using 4:1 hexanes/EtOAc provided **97** (4.7 g).



97

Data for Compound **97:** ^{1}H-NMR (300 MHz, $CDCl_3$): 7.60 (d, 2H, J = 9.3), 6.88 (d, 2H, J = 9.3), 5.53 (m, 2H), 5.43 (m, 1H), 5.36 (t, 1H, J = 10.2), 4.27 (m, 1H), 4.06 (m, 2H), 2.21 (s, 3H), 2.06 (s, 3H), 2.05 (s, 6H).

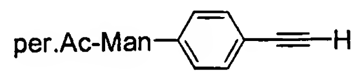
Glycoside **97** (Scheme 16, 4.0 g, 7.27 mmol) was added to a round-bottomed flask along with TMSalkyne (**63**) (5.14 mL, 36.3 mmol), bistriphenylphosphine palladium (II) dichloride (102 mg, 0.15 mmol), copper (I) iodide (14 mg, 0.073 mmol), triethylamine (3.0 mL, 21.8 mmol), and DMF (30 mL). The mixture was stirred at rt under N_2 for 10 h. The crude was then added to EtOAc (200 mL) and washed with H_2O (150 mL), NH_4Cl (150 mL), and brine (150 mL), dried over $MgSO_4$, filtered, and concentrated to dryness. Purification by flash chromatography using 4:1 hexanes/EtOAc provided **98** (2.5 g).



98

Data for Compound **98**: ^{1}H-NMR (300 MHz, $CDCl_3$): 7.42 (d, 2H, J = 9.2), 7.02 (d, 2H, J = 9.3), 5.54 (m, 2H), 5.44 (m, 1H), 5.36 (t, 1H, J = 9.9), 4.28 (m, 1H), 4.06 (m, 2H), 2.21 (s, 3H), 2.06 (s, 3H), 2.05 (s, 6H), 0.25 (s, 9H).

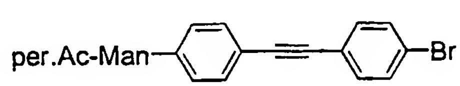
Alkyne **98** (Scheme 16, 2.49g, 4.78 mmol) was charged to a round-bottomed flask along with THF (10 mL). To this was added TBAF (1.0 M in THF, 5.7 mL, 5.7 mmol) and the reaction was stirred under N_2 for 1.5 h. The crude mixture was added to water (50 mL) and extracted with CH_2Cl_2 (2 X 100 mL). Organics were then washed with brine (200 mL), dried over $MgSO_4$, filtered, and concentrated to dryness. The crude was dried *in vacuo* to provide **99** (2.0 g).



99

Data for **99**: ^{1}H-NMR (300 MHz, $CDCl_3$): 7.44 (d, 2H, J = 8.7), 7.04 (d, 2H, J = 8.7), 5.55 (m, 2H), 5.44 (m, 1H), 5.37 (t, 1H, J = 10.2), 5.28 (m, 1H), 4.06 (m, 2H), 3.04 (s, 1H), 2.21 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H).

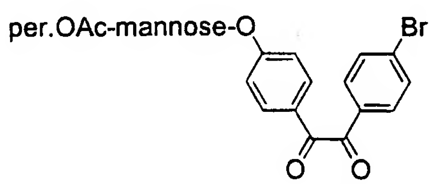
Alkyne **99** (Scheme 16, 2.0 g, 4.46 mmol) was charged to a round-bottomed flask along with DMF (20 mL), 4-bromo-1-iodobenzene **86** (1.5 g, 5.35 mmol), copper iodide (9.0 mg, 0.045 mmol), dichlorobis(triphenyl-phosphine) palladium(II) (63 mg, 0.09 mmol) and triethylamine (2.0 mL, 13.4 mmol). The reaction mixture was stirred at rt under an atmosphere of nitrogen for 8 h. The crude reaction mixture was added to a mixture of ethyl acetate (100 mL), and washed with NH_4Cl (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated to dryness. The crude was purified by flash column chromatography using 4:1 to 2:1 hexanes/EtOAc providing **100** (420 mg).



100

Data for compound **100**: ^{1}H-NMR (300 MHz, $CDCl_3$): 7.54 (d, 2H, J = 8.4), 7.47 (d, 2H, J = 8.1), 7.23 (d, 2H, J = 8.7), 7.05 (d, 2H, J = 8.6), 5.54 (m, 2H), 5.44 (m, 1H), 5.36 (m, 1H), 4.27 (m, 1H), 4.06 (m, 2H), 2.21 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H).

Alkyne **100** (Scheme 16, 430 mg, 0.7 mmol) was charged to a round-bottomed flask along with CCl_4 (4.0 mL), CH_3CN (4.0 mL), H_20 (6.0 mL), and sodium periodate (610 mg, 2.85 mmol). After stirring for 5 min, ruthenium dioxide (2.0 mg, 0.016 mmol) was added and the mixture stirred at rt for 6 h. The crude was added to CH_2Cl_2 (100 mL), washed with H_2O (2 X 55 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated to dryness. The crude was flashed using 1:1 hexanes/ethyl acetate to provide **101** as a white solid (425 mg).

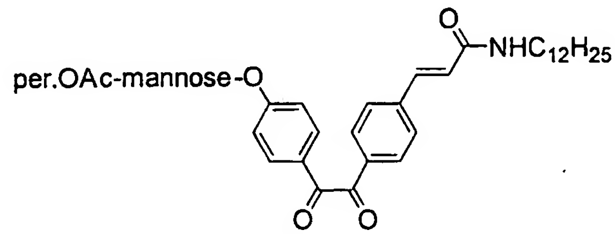


101

Data for Compound **101**: ^{1}H-NMR (300 MHz, $CDCl_3$): 7.98 (d, 2H, J = 8.5), 7.85 (d, 2H, J = 8.6), 7.68 (d, 2H, J = 8.4), 7.21 (d, 2H, J = 8.5), 5.62 (m, 1H), 5.57 (m, 1H), 5.48 (m, 1H), 5.39 (m, 1H), 4.24 (m, 1H), 4.02 (m, 2H), 2.21 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H).

Dione **101** (Scheme 16, 0.4 g) was added to a round-bottomed flask along with **57i** (226 mg, 0.95 mmol), DMF (10 mL), palladium (II) acetate (5.0 mg, 0.02 mmol), tri-*o*-tolylphosphine (23 mg, 0.08 mmol), and triethylamine

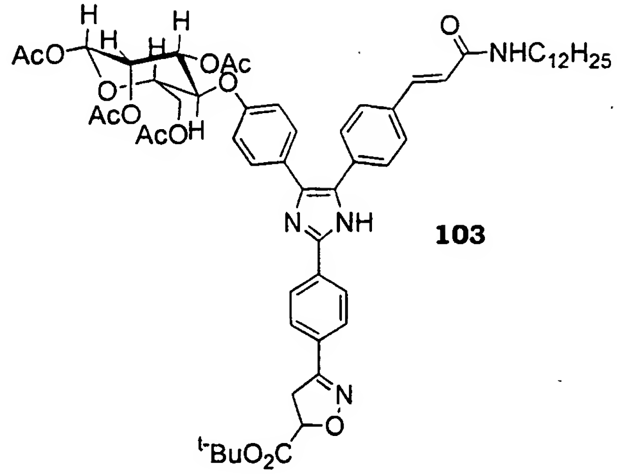
(26 μL). The resultant reaction mixture was heated to 100 °C for 1.5 h. The crude was added to CH_2Cl_2 (75 mL), washed with H_2O (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated to dryness. Flash Chromatography using 1:1 hexanes to ethylacetate provided **102** (302 mg) as a yellow solid.



102

Data for Compound **102**: ^{1}H-NMR (300 MHz, $CDCl_3$): 7.98 (d, 2H, J = 8.6), 7.61 (m, 4H), 7.21 (m, 3H), 6.48 (d, 1H, J = 15.4), 5.62 (m, 1H), 5.57 (m, 1H), 5.47 (m, 1H), 5.40 (m, 1H), 4.28 (m, 1H), 4.05 (m, 2H), 3.20 (m, 2H), 2.21 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 1.59 (m, 2H), 1.22 (m, 18H), 0.82 (m, 3H).

Dione **102** (Scheme 16, 250 mg, 0.32 mmol) was added to a round-bottomed flask along with **34a** (81 mg, 0.35 mmol), NH_4OAc (0.74 g, 9.6 mmol), and HOAc (5 mL), and the mixture was heated to 100 °C under N_2 for 1.2 h. The crude material was added to ethyl acetate (50 mL), washed with H_2O (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated to dryness. The crude material was eluted on a preparative TLC plate (1.0 mm) using 10:1 CH_2Cl_2/MeOH to provide **103** (178 mg) as a yellow solid.



103

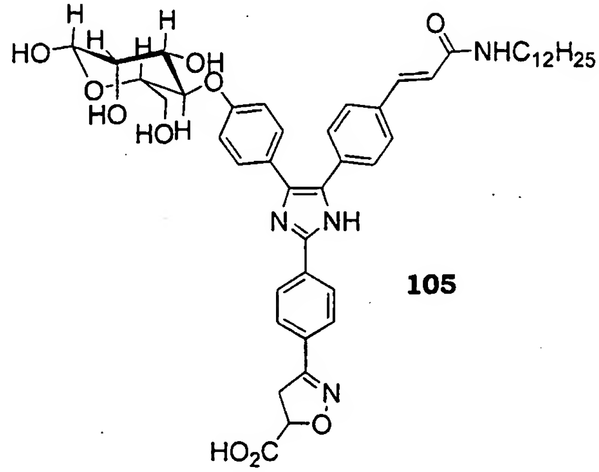
Data for compound **103**: ^{1}H-NMR (300 MHz, $CDCl_3$): 8.1 (d, 2H, J = 8.4), 7.98 (m, 1H), 7.78 (d, 2H, J = 8.6), 7.45 (m, 5H), 7.40 (d, 2H, J = 8.2), 7.06 (d, 2H, J = 8.5), 6.38 (d, 1H, J = 15.2), 5.58 (m, 2H), 5.40 (m, 2H), 5.10 (t, 1H, J = 11.2), 4.29 (m, 1H), 4.08 (m, 2H), 3.60 (m, 2H), 3.38 (m, 2H), 2.21 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 1.57 (s, 9H), 1.23 (m, 21H), 0.87 (m, 3H).

Imidazole **103** (Scheme 16, 150 mg) was added to a round-bottomed flask along with 20% TFA in CH_2Cl_2 (2 mL) and stirred at rt under N_2 for 1.5 h. The crude, which was a mixture of **104** and **105** (see example 88) was concentrated to dryness and chromatographed by preperative TLC (1.0 mm) using 10:1 CH_2Cl_2/MeOH to provide **104** (12 mg) and **105** (52 mg).

Data for compound **104**: ^{1}H-NMR (300 MHz, $CDCl_3/CD_3OD$): 8.08 (d, 2H, J = 8.4), 7.98 (m, 1H), 7.76 (d, 2H, J = 8.6), 7.45 (m, 5H), 7.40 (d, 2H, J = 8.2), 7.06 (d, 2H, J = 8.5), 6.36 (d, 1H, J = 15.2), 5.54 (m, 1H), 5.10 (t, 1H, J = 11.2), 4.32-3.95 (m, 6H), 3.60 (m, 2H), 3.38 (m, 2H), 1.57 (s, 9H), 1.23 (m, 21H), 0.87 (m, 3H). MS (ESI): 881.2 (100, [M+H]); calcd $C_{50}H_{65}N_4O_{10}$ ([M+H]) 881.52.

Example 88

Compound **105**

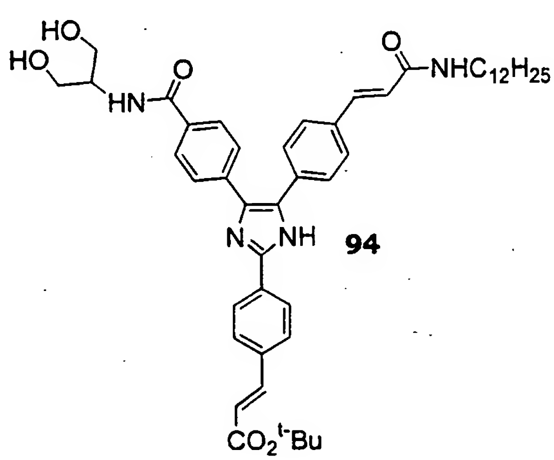


105

Data for Compound **105**: ^{1}H-NMR (300 MHz, CD_3OD): 8.12 (d, 2H, *J* = 8.4), 7.98 (m, 1H), 7.76 (d, 2H, *J* = 8.6), 7.48 (m, 5H), 7.40 (d, 2H, *J* = 8.2), 7.06 (d, 2H, *J* = 8.5), 6.36 (d, 1H, *J* = 15.2), 5.52 (m, 1H), 5.10 (t, 1H, *J* = 11.2), 4.35-3.99 (m, 6H), 3.60 (m, 2H), 3.38 (m, 2H), 1.23 (m, 21H), 0.87 (m, 3H). MS (ESI): 825.7 (100, [M+H]); calcd $C_{46}H_{57}N_4O_{10}$ ([M+H]) 824.39.

Example 89

(E)-3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-[4-(2-hydroxy-1-hydroxymethyl-ethylcarbamoyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-acrylic acid *tert*-butyl ester 94



94

Dione **88** (Scheme 15, R = ^{t}Bu, 0.5 g - see Example 59) was added to a round-bottomed flask along with acrylamide **57i** (305 mg, 2.6 mmol), DMF

(10 mL), palladium (II) acetate (11 mg, 0.08 mmol), tri-*o*-tolylphosphine (52 mg, 0.31 mmol), and triethylamine (0.5 mL). The resultant reaction mixture was heated to 100 °C for 1.5 h. The crude was added to CH_2Cl_2 (75 mL), washed with H_2O (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated to dryness. Flash Chromatography using 3:1 hexanes to ethyl acetate provided Dione **90** (428 mg) as a yellow solid.

Data for dione **90**: ^{1}H-NMR (300 MHz, $CDCl_3$): 8.19 (d, 2H, J = 8.2), 8.0 (d, 2H, J = 8.1), 7.81 (d, 1H, J = 15.7), 7.79 (d, 2H, J = 8.0), 7.07 (d, 2H, J = 8.1), 6.50 (d, 1H, J = 15.8), 5.95 (m, 1H), 3.22 (m, 2H), 1.61 (s, 9H), 1.46 (m, 2H), 1.24 (m, 18H), 0.835 (m, 3H).

Dione **90** (Scheme 15, R = ^{t}-Bu, 405 mg) was charged to a round-bottomed flask and 20% TFA in CH_2Cl_2 (7 mL) was added followed by stirring at rt for 1.5 h. The crude material was concentrated to dryness and dried *in vacuo* to provide carboxylic acid **91** (360 mg) as a light yellow powder.

Data for carboxylic acid **91**: ^{1}H-NMR (300 MHz, DMSO-d_6): 8.18 (d, 2H, J = 8.0), 8.08 (d, 2H, J = 8.0), 7.9 (m, 4H), 7.8 (d, 1H, J = 15.7), 6.52 (d, 1H, J = 15.7), 5.92 (m, H), 3.22 (m, 2H), 1.47 (m, 2H), 1.24 (m, 18H), 0.84 (m, 3H).

Carboxylic acid **91** (Scheme 15, R = ^{t}-Bu, 350 mg) was added to a round-bottomed flask followed by DMF (5 mL), EDCI (137 mg, 0.7 mmol), and serinol (**92**) (130 mg, 1.4 mmol), and the mixture was stirred at rt for 36 h. The crude was added to ethyl acetate (100 mL) and washed with H_2O (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated to

dryness. Flash chromatography using 10:1 CH_2Cl_2/MeOH as eluent provided **93** as a yellow oil (248 mg).

Data for Dione **93**: ^{1}H-NMR (300 MHz, $CDCl_3$): 8.09 (d, 2H, J = 8.2), 7.89 (m, 4H), 7.78 (m, 3H), 6.53 (d, 1H, J = 15.5), 5.95 (m, 1H), 3.65-3.5 (m, 4H), 3.2-3.14 (m, 5H), 1.45 (m, 2H), 1.25 (m, 18H), 0.91 (m, 3H).

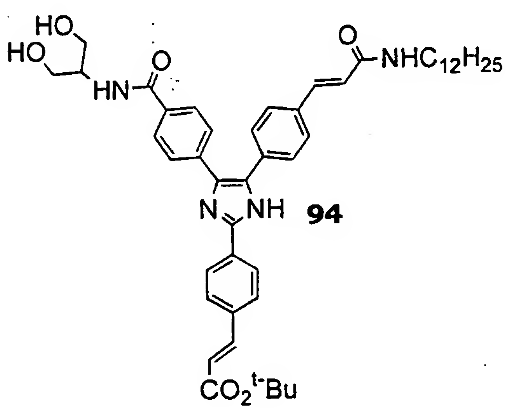
Dione **93** (Scheme 15, R = ^{t}-Bu, 240 mg) was added to a round-bottomed flask along with **34a** (99 mg, 0.43 mmol), NH_4OAc (0.98 g, 13.1 mmol), and HOAc (6 mL), and the mixture was heated to 100 °C under N_2 for 1.2 h. The crude material was added to ethyl acetate (50 mL), washed with H_2O (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated to dryness. The crude material was eluted on a preparative TLC plate (1.0 mm) using 10:1 CH_2Cl_2/MeOH to provide *(E)-3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-[4-(2-hydroxy-1-hydroxymethyl-ethylcarbamoyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-acrylic acid tert-butyl ester* **94** (132 mg) as a yellow solid.

Data for *(E)-3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-[4-(2-hydroxy-1-hydroxymethyl-ethylcarbamoyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-acrylic acid tert-butyl ester* **94**: ^{1}H-NMR (300 MHz, $CDCl_3$): 8.19 (d, 2H, J = 8.1), 7.91 (m, 4H), 7.79(d, 2H, J = 8.0), 7.62 (m, 6H), 6.63 (m, 2H), 5.93 (m, 1H), 3.64-3.52 (m, 4H), 3.21-3.11(m, 5H), 1.61 (s, 9H), 1.45 (m, 2H), 1.22 (m, 18H), 0.82 (m, 3H). MS (ESI): 777.3 (100, [M+H]); calcd $C_{47}H_{60}N_4O_6$ ([M+H]) 777.5.

Example 90

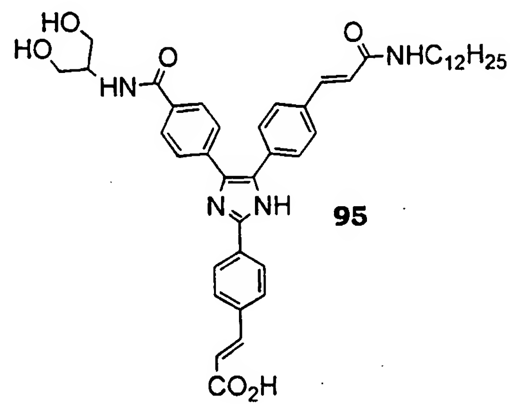
(E)-3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-[4-(2-hydroxy-1-hydroxymethyl-ethylcarbamoyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-acrylic acid 95

Example 89



94

Example 90



95

Imidazole **94** (Scheme 15, R = ^{t}-Bu, 100 mg) was added to a round-bottomed flask along with 20% TFA in CH_2Cl_2 (2 mL) and stirred at rt under N_2 for 1.5 h. The crude material was concentrated to dryness and chromatographed by preperative TLC (1.0 mm) using 8:1 CH_2Cl_2/MeOH to provide *(E)-3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-[4-(2-hydroxy-1-hydroxymethyl-ethylcarbamoyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-acrylic acid* **95** (43 mg).

Data for *(E)-3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-[4-(2-hydroxy-1-hydroxymethyl-ethylcarbamoyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-acrylic acid* **95**: ^{1}H-NMR (300 MHz, DMSO-d$_6$): 8.19 (d, 2H, J = 8.1), 7.91 (m, 4H), 7.78 (d, 2H, J = 8.0), 7.60 (m, 6H), 6.63 (m, 2H), 5.93 (m, 1H), 3.64-3.52 (m, 4H), 3.21-3.11(m, 5H), 1.45 (m, 2H), 1.22 (m, 18H), 0.82 (m, 3H). MS (ESI): 721.6 (100, [M+H]); calcd $C_{43}H_{52}N_4O_6$ ([M+H]) 720.43

Biological Assay

The biological activity of Formulas 1, 2 and 3 is determined by the following procedures:

Materials and Methods

P-selectin ELISA Assay

An ELISA-type assay was used to screen for inhibitors of selectin-ligand interactions. A P-selectin-IgG chimera, constructed as described by Foxall and colleagues (Foxall *et al.*, *FASEB* 117: 895 (1992)), and sialyl-Lewis^X pentaceramide were obtained from Kanebo, Ltd. (Osaka) (Kiyoi *et al.*, *Bioorg. Med. Chem.* 6: 587 (1998)).

Assays were performed essentially as described (Ohmoto *et al.*, *J. Med. Chem.* 39: 1339 (1996)). Polystyrene microtiter plates (Falcon Pro-Bind) were coated with the sialyl-Lewis^X analog at 40-100 pmol/well. Coated wells were blocked with 5% bovine serum albumin (BSA) in 50 mM imidazole buffer, pH 7.2, for 1 hour at room temperature.

Compounds were diluted from DMSO stock solutions in assay buffer (50 mM imidazole buffer, pH 7.2, containing 1% BSA and 1 mM $CaCl_2$). Compounds were always run in duplicate or triplicate. A complex consisting of P-selectin IgG chimera, biotinylated goat F(ab')2 anti-human IgG, and streptavidin-alkaline phosphatase conjugate was made in assay buffer. Selectin chimera was omitted from the complex for negative control ("background") wells. The complex and the test compounds (or vehicle controls) were combined in wells of a polypropylene microtiter plate and incubated for 30 minutes at room temperature. The complex-compound mixture was then added to the blocked, sialyl-Lewis^X-ceramide coated plate and allowed to incubate for 45 minutes at 37°C. After washing 3-4 times with

50 mM imidazole, the bound complex was detected using the colorimetric phosphatase substrate, p-nitrophenylphosphate, at 1 mg/mL in 1 M diethanolamine containing 0.01% $MgCl_2$. After developing for 1-2 hours at room temperature, the absorbance at 405 nM was measured in a Molecular Devices microplate reader. Percent inhibition was calculated by comparing the test compound result with the vehicle control after subtracting the background from each. IC_{50} values were calculated by in-house data analysis software (OntoASSAY; Ontogen, Corp.) using standard algorithms.

Cell-Selectin Adhesion Assays

The ability of compounds to inhibit the adhesion of HL60 cells to purified selectin proteins was measured using a "cell-selectin" assay. Recombinant soluble P- and E-selectin proteins purchased from R&D Systems (Minneapolis, MN) were diluted to 2.5 μg/mL in Dulbecco's PBS containing calcium and magnesium (PBS^+). Falcon Pro-Bind microtiter plate wells were incubated with 50 μL of the P- or E-selectin protein solution for 1 hr at 37°C or overnight at 4°C. The selectin protein was omitted from negative control ("background") wells. Coated wells were then washed three times with PBS^+ and then blocked with 1% BSA in PBS^+ for 1 hour at room temperature. After blocking, the plates were washed 3 times with PBS^+. Compounds were diluted to 2x final test concentration in PBS^+ and added to the blocked, selectin-coated wells in a volume of 50 μL. Samples were always run in duplicate or triplicate. Compounds and vehicle controls were pre-incubated in the wells for ~20 minutes at room temperature.

HL60 cells obtained from the ATCC (Manassas, VA) were cultivated in RPMI medium containing 10% heat-inactivated fetal bovine serum (FBS). For

the assay, cells were harvested by centrifugation, washed once with PBS+, and resuspended in PBS+ at a concentration of 2 x 10^6 cells/mL. Cells were added directly to the compound-containing wells in a volume of 50 μL per well, bringing the compound to its final test concentration in a total volume of 100 μL. Cells and compound were incubated on the selectin-coated wells for 45 minutes at 37°C. Unbound cells were removed using a vacuum manifold and a single wash with 200 μL PBS+ (added slowly using a manual multichannel pipettor). Retained cells were labeled directly on the plate by adding 5 μg/mL of the membrane-permeable fluorescent dye, calcein-AM, and incubating for 30 minutes at 37°C. Signal was quantified in a Wallac Victor fluorescent microplate reader using 485 nM excitation and 535 nM emission. Percent inhibition and IC_{50} values were calculated as described above for the ELISA assay.

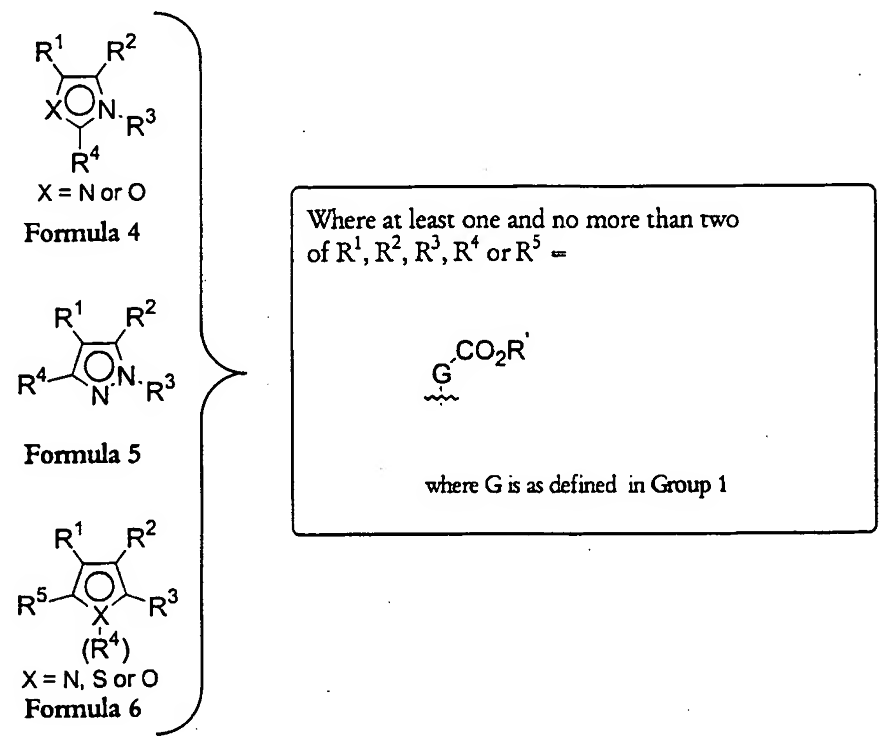
The results which show inhibitory activity of compounds of the current invention against the selectins, are tabulated in Table 3 below:

Table 3

Example	**Compound number**	P-Selectin ELISA	P-Selectin Cell	E-Selectin Cell
		Mean IC50 in uM	Mean IC50 in uM	Mean IC50 in uM
2	**191**	27.7	-	-
3	**192**	7	-	-
4	**193**	34.4	50.5	-
5	**194**		9.6	-
6	**195**	18.1	-	-
7	**196**	1.9	-	-
8	**197**	5.5	-	-
10	**199**	1.8	-	-
11	**200**	53.3	-	-
13	**202**	93.7	21	-
14	**203**	54.3	-	-

15	**204**	33.8	-	-
16	**205**	68.3	-	-
17	**206**	40.1	-	-
19	**208**	12.6	71	-
21	**210**	0.43	15.7	-
23	**212**	8	22.3	-
24	**213**	2.3	-	-
26	**215**	2.6	-	-
27	**216**	2.9	36.8	-
28	**217**	5.5	18.7	-
29	**218**	-	19.8	-
30	**219**	0.83	-	-
31	**220**	7	23.5	-
33	**222**	-	10.7	-
35	**224**	-	18.4	-
36	**225**	-	25.6	-
37	**226**	26.1	8.8	-
39	**228**	-	18.1	62.3
42	**231**	-	20.6	41.5
44	**233**	-	4.7	-
45	**234**	-	54.4	-
47	**236**	4.7	1.1	-
49	**238**	179.5	36	-
50	**239**	5.8	-	-
52	**241**	4	-	21.5
54	**243**	8.6	11.2	-
56	**245**	8.2	29.5	-
58	**247**	97.8	32.1	-
59	**111**	23.5	-	-
60	**248**	26.3	30.6	-
62	**250**	17.2	-	-
63	**251**	82	-	-
65	**253**	0.3	9.4	34.3
68	**256**	0.3	-	60.6
67	**255**	0.38	120.5	-
69	**257**	14.1	46.6	-
70	**258**	3.1	-	18
71	**259**	2.3	-	-
72	**260**	-	28	-
73	**261**	-	3.2	37.7
75	**263**	4.7	21.4	-
77	**265**	26.1	70.5	-
79	**267**	16.2	44.4	-
81	**269**	-	21.8	-
83	**270**	0.65	15.8	-
84	**147**	4.5	51.4	55.8
86	**82**	-	17.7	-
87	**104**	19.7	-	-
89	**94**	86.6	-	-
90	**95**	1.9	-	-

Included within the scope of this invention are prodrugs of Formulas 1, 2 and 3. In the case of the -COOH being present, pharmaceutically acceptable esters can be employed. These include, but are not limited to, compounds such as Formulas 4, 5 and 6, where R' can be methyl, ethyl, *tert*-butyl, pivaloyloxymethyl, and the like, and those esters known in the art for modifying solubility or hydrolysis characteristics for use as sustained release or prodrug formulations.



Formulas 4, 5 and 6

Pharmaceutically acceptable salts of the compounds of Formulas 1, 2 and 3, where a basic or acidic group is present in the structure, are also included within the scope of this invention. When an acidic substituent is present, such as -COOH, there can be formed the ammonium, morpholinium, sodium, potassium, barium, calcium salt, and the like, for

use as the dosage form. When a basic group is present, such as amino or a basic heteroaryl radical, such as pyridyl, an acidic salt, such as hydrochloride, hydrobromide, phosphate, sulfate, trifluoroacetate, trichloroacetate, acetate, oxalate, maleate, pyruvate, malonate, succinate, citrate, tartarate, fumarate, mandelate, benzoate, cinnamate, methane-sulfonate, ethanesulfonate, picrate and the like, and include acids related to the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2 (1977) p.1-19 and incorporated herein by reference, can be used as the dosage form.

In addition, some of the compounds of the present invention may form solvates with water or common organic solvents. Such solvates are encompassed within the scope of the invention.

The term "therapeutically effective amount" shall mean that amount of drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor or others.

The present invention provides a method of administering a compound selected from those defined in Formulas 1, 2 and 3 above in cases where inhibition or modulating selectin activity in a body is needed. These conditions include but are not limited to the foregoing described diseases.

To administer Formulas 1, 2 and 3, the compounds may be administered orally as tablets, aqueous or oily suspensions, lozenges, troches, powders, granules, emulsions, capsules, syrups or elixirs. The composition for oral use may contain one or more agents selected from the group of sweetening agents, flavoring agents, coloring agents and preserving

agents in order to produce pharmaceutically elegant and palatable preparations. The tablets contain the acting ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, (1) inert diluents, such as calcium carbonate, lactose, calcium phosphate or sodium phosphate; (2) granulating and disintegrating agents, such as corn starch or alginic acid; (3) binding agents, such as starch, gelatin or acacia; and (4) lubricating agents, such as magnesium stearate, stearic acid or talc. These tablets may be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. Coating may also be performed using techniques described in the U.S. Patent Nos. 4,256,108; 4,160,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may be in the form of hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. They may also be in the form of soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions normally contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspension. Such excipients may be (1) suspending agent such as sodium carboxymethyl cellulose, methyl cellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; (2) dispersing or wetting agents which may be (a) naturally occurring

phosphatide such as lecithin; (b) a condensation product of ethylene oxide with a fatty acid, for example, polyoxyethylene stearate; (c) a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadecaethylen-oxycetanol; (d) a condensation product of ethylene oxide with a partial ester derived from a fatty acid and hexitol such as polyoxyethylene sorbitol monooleate, or (e) a condensation product of ethylene oxide with a partial ester derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate.

The pharmaceutical composition may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to known methods using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of the invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperature but liquid at the rectal temperature and will

therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

The compounds of the present invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidyl-cholines.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of Formulas 1, 2 and 3 are employed.

The compounds of Formulas 1, 2 and 3 may also be administered directly into the lungs by inhalation or intranasal delivery when formulated in a solvent that is suitable for aerosol formation. Such delivery would be useful for direct delivery to the site of action, as in asthma. However, because administration to the lungs may result in significant blood levels of the compound, this route of administration can be also used in cases where systemic exposure is required.

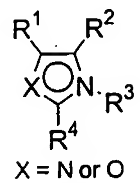
Dosage levels of the compounds of the present invention are of the order of about 0.5 mg to about 100 mg per kilogram body weight, with a preferred dosage range between about 20 mg to about 50 mg per kilogram body weight per day (from about 25 mg to about 5 g's per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for oral administration to humans may contain 5 mg to 1 g of an active compound with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the

total composition. Dosage unit forms will generally contain between from about 5 mg to about 500 mg of active ingredient.

It will be understood however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, gender, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy. The dosage needs to be individualized by the clinician.

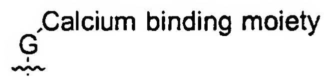
We claim:

1. A compound having the structural Formula 1a:



Formula 1a

Where at least one and no more than two of R^1, R^2, R^3, R^4 or R^5 =

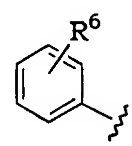


as defined in **Group 1**

Case A: When one of R^1, R^2, R^3, or R^4 is selected from **Group I** (templates **1-6**):

Group I is defined in Figure 1, Table 1, below:

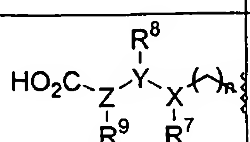
Group I =

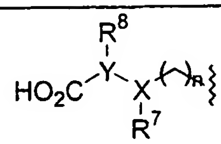
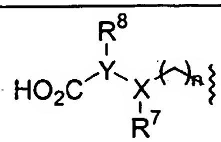
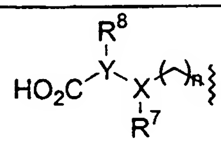
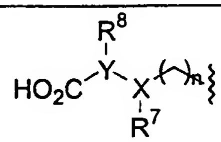


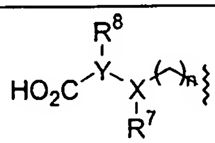
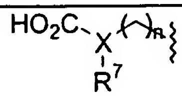
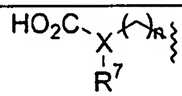
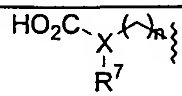
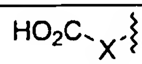
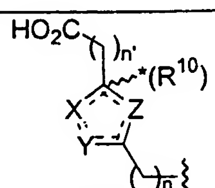
where R^6 equals one of the following in Table 1:

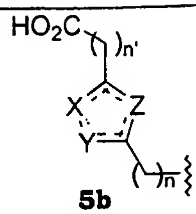
Figure 1

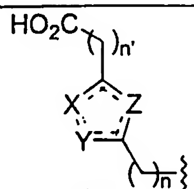
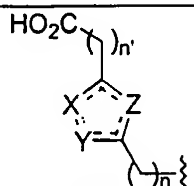
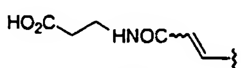
Table 1

R^6 Type	**Template**	**Atom or group**					
		X	**Y**	**Z**	**R^7**	**R^8**	**R^9**
i	 **1**	C	N	CH	=O	H	$(CH_2)_{n'}OH$

ii	 **2a**	CH	$(CH_2)_{n'}$	-	$(CH_2)_{n''}CO_2H$	-	-
iii	 **2b**	N	C	-	H	=O	-
iv	 **2c**	CH	CH	-	-OH	-OH	-
v	 **2d**	N	$(CH_2)_{n'}$	-	-H	-	-

R6 Type	Template	Atom or group					
		X	Y	Z	R7	R8	R9
vi	 **2e**	O	$(CH_2)_{n'}$	-	-	-	-
vii	 **3a**	C	-	-	=O	-	-
viii	 **3b**	CH	-	-	-OH	-	-
ix	 **3c**	CH	-	-	$-NH_2$	-	-
x	 **4a**	$(CH_2)_{n'}$	-	-	-	-	-
xi	 **5a**	O	N	CH *(no R^{10}) or CH_2 *(R^{10}=H)	-	-	-

xii	 5b	S, O or NH	CH	N	-	-	-

R^6 Type	Template	Atom or group					
		X	**Y**	**Z**	**R^7**	**R^8**	**R^9**
xiii	 **5c**	N	CH	S, O, or NH	-	-	-
xiv	 **5d**	CH	S, O, or NH	N	-	-	-
xv	 **6a**	-	-	-	-	-	-

(n", and/or n' and/or n can be 0, 1, 2, 3, 4, 5 or 6)

and one of R^1, R^2, R^3, or R^4 must be selected from **Group II**:

Group II is defined as one of the following:

(i) $C_{0\text{-}6}CO_2R^{11}$, $C_{0\text{-}6}CONHR^{11}$, $C_{0\text{-}6}NHCOR^{11}$, $C_{0\text{-}6}NHC(O)NHR^{11}$, $C_{0\text{-}6}NHSO_2R^{11}$, wherein R^{11} is $C_{8\text{-}16}$ alkyl, or $C_{3\text{-}8}$ alkylaryl, in which the said aryl group is mono- or disubstituted with a member selected from the group consisting of hydrogen, hydroxy, halo, $C_{1\text{-}6}$ alkyl and $C_{1\text{-}6}$ alkyloxy, $C_{1\text{-}6}$ cycloalkyloxy, or C_1-C_4 alkyl aryl or C_1-C_4 alkoxy aryl, in which said aryl group is either unsubstituted, mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, $C_{1\text{-}4}$ alkyl, or $C_{1\text{-}4}$ alkyloxy; or

(ii) substituted or unsubstituted C_{8-16} alkyl or substituted C_{8-16} alkenyl, wherein the substituents are selected from the group consisting of hydrogen, hydroxy, C_{1-6} alkyloxy, amino, C_{1-6} alkylamino, or C_{1-6} dialkylamino, or aryl; or

(iii) Unsubstituted, mono-, di-, or tri-substituted aryl-C_{0-11} alkyl wherein aryl is selected from the group consisting of phenyl, or pyridino, wherein the substituents are selected from the group consisting of:

(a) $C_{0-6}CO_2R^{12}$, $C_{0-6}CON(^*H)R^{12}$, $C_{0-6}NHSO_2R^{12}$, *trans*-$CH{=}CHCO_2R^{12}$, *trans*-$CH{=}CHCON(^*H)R^{12}$, or cyclopropyl$CON(^*H)R^{12}$ wherein R^{12} is C_{8-16} alkyl, bis-C_{4-16} alkyl (* no H), *N*-(methyl) C_{8-16} alkyl (* no H), C_{8-16} alkyloxyalkyl, C_{0-3} alkyl C_{7-10} perfluoroalkyl, C_{5-8} cycloalkyl, C_{2-11} alkylaryl, C_{1-5} alkylaryl C_{1-8} alkyl, aminoaryl, C_{0-4} alkyltetrahydrofurfuryl, C_{0-4} alkyldiphenylmethyl which the said alkyl group or said aryl group is unsubstituted, mono- or disubstituted with a member selected from the group consisting of hydroxy, carboxy, halo, C_{1-6} alkyl and C_{1-6} alkyloxy, C_{1-6} cycloalkyloxy, C_1-C_4 alkyl aryl or C_1-C_4 alkoxy aryl, in which said aryl group is either unsubstituted, mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-4} alkyl, or C_{1-4} alkyloxy; or R^{10} can be N-Boc-piperidino, or N-carboethoxypiperidino;

And one of R^1, R^2, R^3, or R^4 must be selected from **Group III**:

Group III is defined as either:

(i) Hydrogen; or

(ii) Unsubstituted, mono or disubstituted C_{1-16} alkyl, C_{0-16} alkylamino, amino C_{0-16} alkyl, C_{0-6} alkylcarboxyl or C_{0-6} alkyl carboxyl ester, C_{0-16} alkyloxyalkyl or C_{2-16} alkenyl wherein the substituents are independently selected from the group consisting of hydroxy, C_{1-8} alkyl, C_{1-8} alkyloxyalkyl, C_{1-8} alkylthioalkyl, phenyl-C_{1-8} alkylamino, C_{1-8} alkoxycarbonyl; or C_{0-6} carboxyl, triazole, 2,3-(methylenedioxy)benzyl; or

(iii) substituted or unsubstituted N or C-linked pyrrolidino, piperidino, piperidonyl, morpholino, piperazino, N-Boc-piperazino, N-C_{1-10} alkylpiperazino, N-C_{3-6} alkenylpiperazino, N-(C_{1-6} alkoxy C_{1-6} alkyl)piperazino, N-(C_{1-6} alkoxy C_{3-6} alkenyl)piperazino, N-(C_{1-6} alkylamino C_{1-6} alkyl)piperazino, N-(C_{1-6} alkylamino C_{3-6} alkenyl)piperazino, uracil or other purine or pyrimidine heterocycles, wherein the substituents are N or C-linked, and are independently selected from:

(a) substituted C_{1-16} alkyloxy, C_{3-16} alkenyloxy, substituted C_{3-16} alkynyloxy; or

(b) substituted C_{1-6} alkyl-amino, di(substituted C_{1-6} alkyl)amino; or

(c) CONHC_1-C_{16} alkyl, COOC_1-C_{16} alkyl, C_{0-11} alkylCO_2H, $C_{0-11}NHC(O)NHR^{11}$, $C_{0-11}NHSO_2R^{11}$, *trans*- $CH{=}CHCO_2R^{11}$, or *trans*- $CH{=}CHCONHR^{11}$ wherein R^{11} is hydrogen, C_{1-16} alkyl, or C_{1-16} alkyl aryl, in which the said aryl group, is mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-6} alkyl and C_{1-6} alkyloxy, C_{1-6} cycloalkyloxy, or C_1-C_4 alkyl aryl or C_1-C_4 alkoxy aryl in

which said aryl group is either unsubstituted, mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-4} alkyl, C_{1-4} alkyloxy, and aryl; or

(iv) either unsubstituted, mono-, di, or tri-substituted aryl, or C_0-C_{12} aryl, wherein the substituents are independently selected from;

(a) hydroxy, halo; or

(b) unsubstituted or substituted C_{0-3} alkyloxy C_{0-3} alkyl, C_{3-16} alkenyloxy, substituted C_{3-16} alkynyloxy, aryl; or

(c) mono or di-substituted C_{1-6} alkyl-amino, di(substituted C_{1-6} alkyl)amino; or

(d) $CONHC_1$-C_{16} alkyl, $COOC_1$-C_{16} alkyl, C_{0-11} alkylCO_2H, $C_{0-11}NHC(O)NHR^{11}$, $C_{0-11}NHSO_2R^{11}$, *trans*- $CH=CHCO_2R^{11}$, or *trans*- $CH=CHCONHR^{11}$ wherein R^{11} is hydrogen, C_{1-16} alkyl, or C_{1-16} alkyl aryl, in which the said aryl group, is mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-6} alkyl and C_{1-6} alkyloxy, C_{1-6} cycloalkyloxy, or C_1-C_4 alkyl aryl or C_1-C_4 alkoxy aryl in which said aryl group is either unsubstituted, mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-4} alkyl, C_{1-4} alkyloxy, and aryl.

(e) O- or C-linked hexose or furanose.

and one of R^1, R^2, R^3, or R^4 must be selected from **Group IV**:

Group IV is defined as either:

(i)hydrogen; or

(ii)substituted or unsubstituted C_{1-16} alkyl or C_{2-12} alkenyl wherein the substituents are independently selected from the group consisting of hydroxy, C_{1-6} alkyloxy, C_{1-6}alkylthio, C_{1-6} alkylamino, phenyl-C_{1-6} alkylamino, C_{1-6} alkoxycarbonyl; or

(iii) mono, di or tri-substituted aryl C_{0-4} alkyl or substituted C_{0-4} alkyl aryl, wherein the aryl group is selected from phenyl, imidazolyl, indolyl, furyl, thienyl or pyridyl in which the substituents are selected from:

(a)hydrogen; or

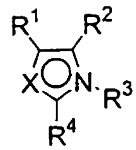
(b)hydroxy or halo

The remaining R group must be either unsubstituted or be equal to Hydrogen.

Case B: When two of R^1, R^2, R^3, or R^4 are selected from **Group I** (templates **1-6**), one of R^1, R^2, R^3, or R^4 must be selected from **Group II**, and one of R^1, R^2, R^3, or R^4 must be selected from **Group IV**. The remaining R groups must be either unsubstituted or be equal to Hydrogen; where **Groups I, II, III** and **IV** are defined above;

and the pharmaceutically acceptable salts and esters thereof.

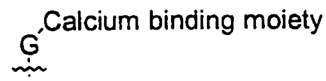
2. We claim a compound having the structural Formula 1b:



X = N or O

Formula 1b

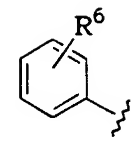
Where at least one and no more than two of R^1, R^2, R^3, R^4 or R^5 =



as defined in **Group 1**

Case A: When one of R^1, R^2, R^3, R^4, or $^*R^5$ (*in General Formula 3) is selected from **Group I** (template **7**):

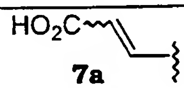
Group I (template 7) is defined in Figure 2, Table 2, below:

Group I = 

where R^6 equals one of the following in Table 2:

Figure 2

Table 2

R^6 Type	Template	Atom or group					
		X	**Y**	**Z**	**R^7**	**R^8**	**R^9**
xvi	 **7a**	-	-	-	-	-	-

one of R^1, R^2, R^3, or R^4 must be selected from **Group V**:

Group **V** is defined as one of the following:

(i) Unsubstituted, mono-, di-, or tri-substituted aryl-$C_{0\text{-}11}$ alkyl wherein aryl is selected from the group consisting of phenyl, or pyridino, wherein the substituents are selected from the group consisting of:

(a) $C_{0\text{-}6}CO_2R^{12}$, $C_{0\text{-}6}CON(*H)R^{12}$, $C_{0\text{-}6}NHSO_2R^{12}$, *trans*-$CH{=}CHCO_2R^{12}$, *trans*-$CH{=}CHCON(*H)R^{12}$, or cyclopropyl$CON(*H)R^{12}$ wherein R^{12} is $C_{8\text{-}16}$ alkyl, bis-$C_{4\text{-}16}$ alkyl (* no H), *N*-(methyl) $C_{8\text{-}16}$ alkyl (* no H), $C_{8\text{-}16}$ alkyloxyalkyl, $C_{0\text{-}3}$ alkyl $C_{7\text{-}10}$ perfluoroalkyl, $C_{5\text{-}8}$ cycloalkyl, $C_{2\text{-}11}$ alkylaryl, $C_{1\text{-}5}$ alkylaryl $C_{1\text{-}8}$ alkyl, aminoaryl, $C_{0\text{-}4}$ alkyltetrahydrofurfuryl, $C_{0\text{-}4}$ alkyldiphenylmethyl which the said alkyl group or said aryl group, are unsubstituted, mono- or

disubstituted with a member selected from the group consisting of hydroxy, carboxy, halo, C_{1-6} alkyl and C_{1-6} alkyloxy, C_{1-6} cycloalkyloxy, C_1-C_4 alkyl.

and one of R^1, R^2, R^3, or R^4 must be selected from **Group VI**.

Group VI is defined as one of the following:

(i) Hydrogen; or

(ii) either unsubstituted, mono-, di, or tri-substituted aryl, or C_0-C_{12} aryl, wherein the substituents are independently selected from;

(a) hydroxy, halo; or

(b) $CONHC_1$-C_{16} alkyl, $CONHC_{1-2}$ bis- C_{2-4} alkyl, $COOC_1$-C_{16} alkyl, C_{0-11} alkylCO_2H, $C_{0-11}NHC(O)NHR^{11}$, $C_{0-11}NHSO_2R^{11}$, *trans*-$CH=CHCO_2R^{11}$, or *trans*- $CH=CHCONHR^{11}$ wherein R^{11} is hydrogen, C_{1-16} alkyl, or C_{1-16} alkyl aryl, in which the said aryl groups, or alkyl groups are mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-6} alkyl and C_{1-6} alkyloxy, C_{1-6} cycloalkyloxy, or C_1-C_4 alkyl aryl or C_1-C_4 alkoxy aryl in which said aryl group is either unsubstituted, mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-4} alkyl, C_{1-4} alkyloxy, and aryl.

(c) O- or C-linked hexose or furanose.

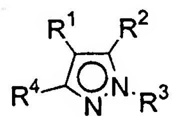
The remaining R groups must be either unsubstituted or be equal to Hydrogen.

Case B: When two of R^1, R^2, R^3, or R^4 are selected from **Group I** (template **7**), one of R^1, R^2, R^3, or R^4 must be selected from **Group V**. The

remaining R groups must be either unsubstituted or be equal to Hydrogen; where **Groups I, II, III, IV, V,** and **VI** are defined above;

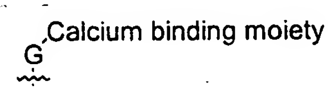
and the pharmaceutically acceptable salts and esters thereof.

3. A compound having the structural Formula 2a:



Formula 2a

Where at least one and no more than two of R^1, R^2, R^3, R^4 or R^5 =

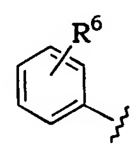


as defined in **Group 1**

Case A: When one of R^1, R^2, R^3, or R^4 is selected from **Group I** (templates **1-6**):

Group I is defined in Figure 1, Table 1, below:

Group I =

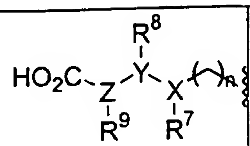
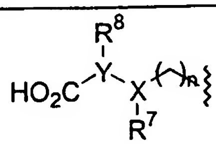
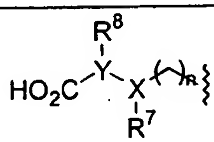
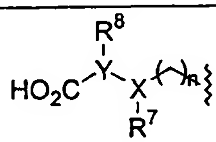
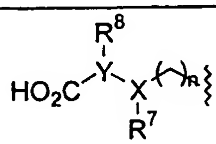


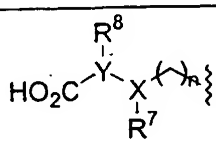
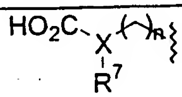
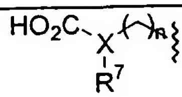
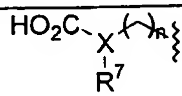
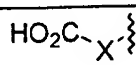
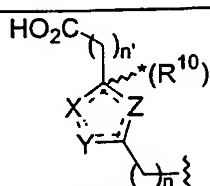
where R^6 equals one of the following in Table 1:

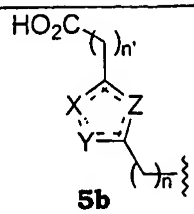
Figure 1

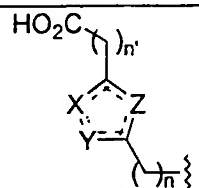
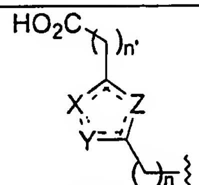
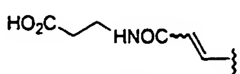
Table 1

R^6 Type	**Template**	**Atom or group**					
		X	**Y**	**Z**	**R^7**	**R^8**	**R^9**

i	 **1**	C	N	CH	=O	H	$(CH_2)_{n'}OH$
ii	 **2a**	CH	$(CH_2)_{n'}$	-	$(CH_2)_{n''}CO_2H$	-	-
iii	 **2b**	N	C	-	H	=O	-
iv	 **2c**	CH	CH	-	-OH	-OH	-
v	 **2d**	N	$(CH_2)_{n'}$	-	-H	-	-

R^6 Type	Template	Atom or group					
		X	**Y**	**Z**	**R^7**	**R^8**	**R^9**
vi	 **2e**	O	$(CH_2)_{n'}$	-	-	-	-
vii	 **3a**	C	-	-	=O	-	-
viii	 **3b**	CH	-	-	-OH	-	-
ix	 **3c**	CH	-	-	$-NH_2$	-	-
x	 **4a**	$(CH_2)_{n'}$	-	-	-	-	-
xi	 **5a**	O	N	CH *(no R^{10}) or CH_2 *(R^{10}=H)	-	-	-

xii	 5b	S, O or NH	CH	N	-	-	-

R^6 Type	Template	Atom or group					
		X	**Y**	**Z**	**R^7**	**R^8**	**R^9**
xiii	 **5c**	N	CH	S, O, or NH	-	-	-
xiv	 **5d**	CH	S, O, or NH	N	-	-	-
xv	 **6a**	-	-	-	-	-	-

(n", and/or n' and/or n can be 0, 1, 2, 3, 4, 5 or 6)

and one of R^1, R^2, R^3, or R^4 must be selected from **Group II**:

Group II is defined as one of the following:

(i) $C_{0-6}CO_2R^{11}$, $C_{0-6}CONHR^{11}$, $C_{0-6}NHCOR^{11}$, $C_{0-6}NHC(O)NHR^{11}$, $C_{0-6}NHSO_2R^{11}$, wherein R^{11} is C_{8-16} alkyl, or C_{3-8} alkylaryl, in which the said aryl group, is mono- or disubstituted with a member selected from the group consisting of hydrogen, hydroxy, halo, C_{1-6} alkyl and C_{1-6} alkyloxy, C_{1-6} cycloalkyloxy, or C_1-C_4 alkyl aryl or C_1-C_4 alkoxy aryl, in which said aryl group is either unsubstituted, mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-4} alkyl, or C_{1-4} alkyloxy; or

(ii) substituted or unsubstituted C_{8-16} alkyl or substituted C_{8-16} alkenyl, wherein the substituents are selected from the group consisting of hydrogen, hydroxy, C_{1-6} alkyloxy, amino, C_{1-6} alkylamino, or C_{1-6} dialkylamino, or aryl; or

(iii) Unsubstituted, mono-, di-, or tri-substituted aryl-C_{0-11} alkyl wherein aryl is selected from the group consisting of phenyl, or pyridino, wherein the substituents are selected from the group consisting of:

(a) $C_{0-6}CO_2R^{12}$, $C_{0-6}CON(^*H)R^{12}$, $C_{0-6}NHSO_2R^{12}$, *trans*-$CH{=}CHCO_2R^{12}$, *trans*-$CH{=}CHCON(^*H)R^{12}$, or cyclopropyl$CON(^*H)R^{12}$ wherein R^{12} is C_{8-16} alkyl, bis-C_{4-16} alkyl (* no H), *N*-(methyl) C_{8-16} alkyl (* no H), C_{8-16} alkyloxyalkyl, C_{0-3} alkyl C_{7-10} perfluoroalkyl, C_{5-8} cycloalkyl, C_{2-11} alkylaryl, C_{1-5} alkylaryl C_{1-8} alkyl, aminoaryl, C_{0-4} alkyltetrahydrofurfuryl, C_{0-4} alkyldiphenylmethyl which the said alkyl group or said aryl group, are unsubstituted, mono- or disubstituted with a member selected from the group consisting of hydroxy, carboxy, halo, C_{1-6} alkyl and C_{1-6} alkyloxy, C_{1-6} cycloalkyloxy, C_1-C_4 alkyl aryl or C_1-C_4 alkoxy aryl, in which said aryl group is either unsubstituted, mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-4} alkyl, or C_{1-4} alkyloxy; or R^{10} can be N-Boc-piperidino, or N-carboethoxypiperidino;

And one of R^1, R^2, R^3, or R^4 must be selected from **Group III**:

Group III is defined as either:

(i) Hydrogen; or

(ii) Unsubstituted, mono or disubstituted C_{1-16} alkyl, C_{0-16} alkylamino, amino C_{0-16} alkyl, C_{0-6} alkylcarboxyl or C_{0-6} alkyl carboxyl ester, C_{0-16} alkyloxyalkyl or C_{2-16} alkenyl wherein the substituents are independently selected from the group consisting of hydroxy, C_{1-8} alkyl, C_{1-8} alkyloxyalkyl, C_{1-8} alkylthioalkyl, phenyl-C_{1-8} alkylamino, C_{1-8} alkoxycarbonyl; or C_{0-6} carboxyl, triazole, 2,3-(methylenedioxy)benzyl; or

(iii) substituted or unsubstituted N or C-linked pyrrolidino, piperidino, piperidonyl, morpholino, piperazino, N-Boc-piperazino, N-C_{1-10} alkylpiperazino, N-C_{3-6} alkenylpiperazino, N-(C_{1-6} alkoxy C_{1-6} alkyl)piperazino, N-(C_{1-6} alkoxy C_{3-6} alkenyl)piperazino, N-(C_{1-6} alkylamino C_{1-6} alkyl)piperazino, N-(C_{1-6} alkylamino C_{3-6} alkenyl)piperazino, uracil or other purine or pyrimidine heterocycles, wherein the substituents are N or C-linked, and are independently selected from:

(a) substituted C_{1-16} alkyloxy, C_{3-16} alkenyloxy, substituted C_{3-16} alkynyloxy; or

(b) substituted C_{1-6} alkyl-amino, di(substituted C_{1-6} alkyl)amino; or

(c) CONHC_1-C_{16} alkyl, COOC_1-C_{16} alkyl, C_{0-11} alkylCO_2H, C_{0-11}NHC(O)NHR^{11}, C_{0-11}NHSO_2R^{11}, *trans*- CH=CHCO_2R^{11}, or *trans*- CH=CHCONHR^{11} wherein R^{11} is hydrogen, C_{1-16} alkyl, or C_{1-16} alkyl aryl, in which the said aryl group, is mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-6} alkyl and C_{1-6} alkyloxy, C_{1-6} cycloalkyloxy, or C_1-C_4 alkyl aryl or C_1-C_4 alkoxy aryl in

which said aryl group is either unsubstituted, mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-4} alkyl, C_{1-4} alkyloxy, and aryl; or

(iv) either unsubstituted, mono-, di, or tri-substituted aryl, or C_0-C_{12} aryl, wherein the substituents are independently selected from;

(a) hydroxy, halo; or

(b) unsubstituted or substituted C_{0-3} alkyloxy C_{0-3} alkyl, C_{3-16} alkenyloxy, substituted C_{3-16} alkynyloxy, aryl; or

(c) mono or di-substituted C_{1-6} alkyl-amino, di(substituted C_{1-6} alkyl)amino; or

(d) $CONHC_1$-C_{16} alkyl, $COOC_1$-C_{16} alkyl, C_{0-11} $alkylCO_2H$, $C_{0-11}NHC(O)NHR^{11}$, $C_{0-11}NHSO_2R^{11}$, *trans*- $CH{=}CHCO_2R^{11}$, or *trans*- $CH{=}CHCONHR^{11}$ wherein R^{11} is hydrogen, C_{1-16} alkyl, or C_{1-16} alkyl aryl, in which the said aryl group, is mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-6} alkyl and C_{1-6} alkyloxy, C_{1-6} cycloalkyloxy, or C_1-C_4 alkyl aryl or C_1-C_4 alkoxy aryl in which said aryl group is either unsubstituted, mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-4} alkyl, C_{1-4} alkyloxy, and aryl.

(e) O- or C-linked hexose or furanose.

and one of R^1, R^2, R^3, or R^4 must be selected from **Group IV**:

Group IV is defined as either:

(i)hydrogen; or

(ii)substituted or unsubstituted C_{1-16} alkyl or C_{2-12} alkenyl wherein the substituents are independently selected from the group consisting of hydroxy, C_{1-6} alkyloxy, C_{1-6}alkylthio, C_{1-6} alkylamino, phenyl-C_{1-6} alkylamino, C_{1-6} alkoxycarbonyl; or

(iii) mono, di or tri-substituted aryl C_{0-4} alkyl or substituted C_{0-4} alkyl aryl, wherein the aryl group is selected from phenyl, imidazolyl, indolyl, furyl, thienyl or pyridyl in which the substituents are selected from:

(a)hydrogen; or

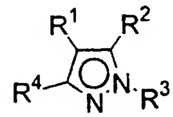
(b)hydroxy or halo

The remaining R group must be either unsubstituted or be equal to Hydrogen.

Case B: When two of R^1, R^2, R^3, or R^4 are selected from **Group I** (templates **1-6**), one of R^1, R^2, R^3, or R^4 must be selected from **Group II**, and one of R^1, R^2, R^3, or R^4 must be selected from **Group IV**. The remaining R groups must be either unsubstituted or be equal to Hydrogen; where **Groups I, II, III** and **IV** are defined above;

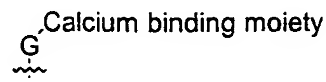
and the pharmaceutically acceptable salts and esters thereof.

4. A compound having the structural Formula 2b:



Formula 2b

Where at least one and no more than two of R^1, R^2, R^3, R^4 or R^5 =

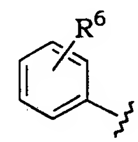


as defined in **Group 1**

Case A: When one of R^1, R^2, R^3, or R^4, is selected from **Group I** (template **7**):

Group I (template 7) is defined in Figure 2, Table 2, below:

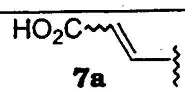
Group I =



where R^6 equals one of the following in Table 2:

Figure 2

Table 2

R^6 Type	Template	Atom or group					
		X	**Y**	**Z**	R^7	R^8	R^9
xvi	 **7a**	-	-	-	-	-	-

one of R^1, R^2, R^3, or R^4 must be selected from **Group V**:

Group **V** is defined as one of the following:

(i) Unsubstituted, mono-, di-, or tri-substituted aryl-$C_{0\text{-}11}$ alkyl wherein aryl is selected from the group consisting of phenyl, or pyridino, wherein the substituents are selected from the group

consisting of:

(a) $C_{0-6}CO_2R^{12}$, $C_{0-6}CON(*H)R^{12}$, $C_{0-6}NHSO_2R^{12}$, *trans*-$CH{=}CHCO_2R^{12}$, *trans*-$CH{=}CHCON(*H)R^{12}$, or cyclopropyl$CON(*H)R^{12}$ wherein R^{12} is C_{8-16} alkyl, bis-C_{4-16} alkyl (* no H), *N*-(methyl) C_{8-16} alkyl (* no H), C_{8-16} alkyloxyalkyl, C_{0-3} alkyl C_{7-10} perfluoroalkyl, C_{5-8} cycloalkyl, C_{2-11} alkylaryl, C_{1-5} alkylaryl C_{1-8} alkyl, aminoaryl, C_{0-4} alkyltetrahydrofurfuryl, C_{0-4} alkyldiphenylmethyl which the said alkyl group or said aryl group, are unsubstituted, mono- or disubstituted with a member selected from the group consisting of hydroxy, carboxy, halo, C_{1-6} alkyl and C_{1-6} alkyloxy, C_{1-6} cycloalkyloxy, C_1-C_4 alkyl.

and one of R^1, R^2, R^3, or R^4 must be selected from **Group VI**.

Group VI is defined as one of the following:

(i) Hydrogen; or

(ii) either unsubstituted, mono-, di, or tri-substituted aryl, or C_0-C_{12} aryl, wherein the substituents are independently selected from;

(a) hydroxy, halo; or

(b) $CONHC_1$-C_{16} alkyl, $CONHC_{1-2}$ bis- C_{2-4} alkyl, $COOC_1$-C_{16} alkyl, C_{0-11} alkylCO_2H, $C_{0-11}NHC(O)NHR^{11}$, $C_{0-11}NHSO_2R^{11}$, *trans*-$CH{=}CHCO_2R^{11}$, or *trans*- $CH{=}CHCONHR^{11}$ wherein R^{11} is hydrogen, C_{1-16} alkyl, or C_{1-16} alkyl aryl, in which the said aryl groups, or alkyl groups are mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-6} alkyl and C_{1-6} alkyloxy, C_{1-6} cycloalkyloxy, or C_1-C_4 alkyl aryl or C_1-C_4 alkoxy aryl in which said aryl group is either

unsubstituted, mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-4} alkyl, C_{1-4} alkyloxy, and aryl.

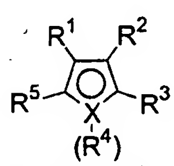
(c) O- or C-linked hexose or furanose.

The remaining R groups must be either unsubstituted or be equal to Hydrogen.

Case B: When two of R^1, R^2, R^3, or R^4 are selected from **Group I** (template **7**), one of R^1, R^2, R^3, or R^4 must be selected from **Group V**. The remaining R groups must be either unsubstituted or be equal to Hydrogen; where **Groups I, II, III, IV, V,** and **VI** are defined above;

and the pharmaceutically acceptable salts and esters thereof.

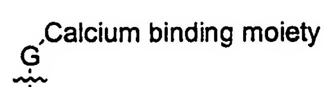
5. A compound having the structural Formula 3a:



X = N, S or O

Formula 3a

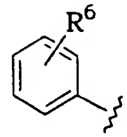
Where at least one and no more than two of R^1, R^2, R^3, R^4 or R^5 =



as defined in **Group 1**

Case A: When one of R^1, R^2, R^3, R^4 or R^5 is selected from **Group I** (templates **1-6**):

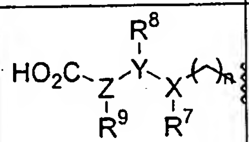
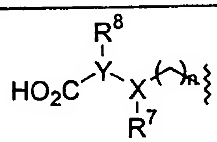
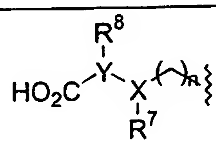
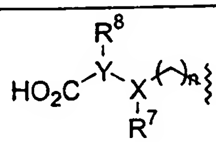
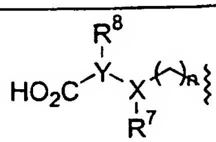
Group I is defined in Figure 1, Table 1, below:

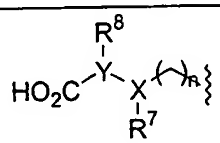
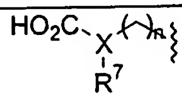
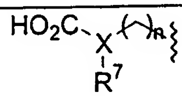
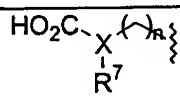
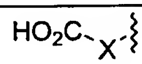
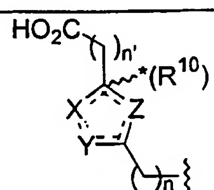
Group I = 

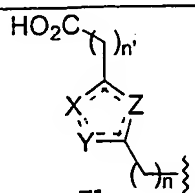
where R^6 equals one of the following in Table 1:

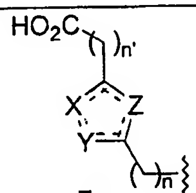
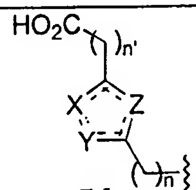
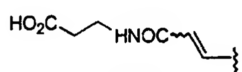
Figure 1

Table 1

R^6 Type	Template	Atom or group					
		X	**Y**	**Z**	**R^7**	**R^8**	**R^9**
i	 **1**	C	N	CH	=O	H	$(CH_2)_{n'}OH$
ii	 **2a**	CH	$(CH_2)_{n'}$	-	$(CH_2)_{n''}CO_2H$	-	-
iii	 **2b**	N	C	-	H	=O	-
iv	 **2c**	CH	CH	-	-OH	-OH	-
v	 **2d**	N	$(CH_2)_{n'}$	-	-H	-	-

R⁶ Type	Template	Atom or group					
		X	**Y**	**Z**	**R^7**	**R^8**	**R^9**
vi	 **2e**	O	$(CH_2)_{n'}$	-	-	-	-
vii	 **3a**	C	-	-	=O	-	-
viii	 **3b**	CH	-	-	-OH	-	-
ix	 **3c**	CH	-	-	$-NH_2$	-	-
x	 **4a**	$(CH_2)_{n'}$	-	-	-	-	-
xi	 **5a**	O	N	CH *(no R^{10}) or CH_2 *(R^{10}=H)	-	-	-

xii	 5b	S, O or NH	CH	N	-	-	-

R^6 Type	Template	Atom or group					
		X	**Y**	**Z**	**R^7**	**R^8**	**R^9**
xiii	 **5c**	N	CH	S, O, or NH	-	-	-
xiv	 **5d**	CH	S, O, or NH	N	-	-	-
xv	 **6a**	-	-	-	-	-	-

(n", and/or n' and/or n can be 0, 1, 2, 3, 4, 5 or 6)

and one of R^1, R^2, R^3, R^4 or R^5 must be selected from **Group II**:

Group II is defined as one of the following:

(i) $C_{0\text{-}6}CO_2R^{11}$, $C_{0\text{-}6}CONHR^{11}$, $C_{0\text{-}6}NHCOR^{11}$, $C_{0\text{-}6}NHC(O)NHR^{11}$, $C_{0\text{-}6}NHSO_2R^{11}$, wherein R^{11} is $C_{8\text{-}16}$ alkyl, or $C_{3\text{-}8}$ alkylaryl, in which the said aryl group, is mono- or disubstituted with a member selected from the group consisting of hydrogen, hydroxy, halo, $C_{1\text{-}6}$ alkyl and $C_{1\text{-}6}$ alkyloxy, $C_{1\text{-}6}$ cycloalkyloxy, or C_1-C_4 alkyl aryl or C_1-C_4 alkoxy aryl, in which said aryl group is either unsubstituted, mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, $C_{1\text{-}4}$ alkyl, or $C_{1\text{-}4}$ alkyloxy; or

(ii) substituted or unsubstituted C_{8-16} alkyl or substituted C_{8-16} alkenyl, wherein the substituents are selected from the group consisting of hydrogen, hydroxy, C_{1-6} alkyloxy, amino, C_{1-6} alkylamino, or C_{1-6} dialkylamino, or aryl; or

(iii) Unsubstituted, mono-, di-, or tri-substituted aryl-C_{0-11} alkyl wherein aryl is selected from the group consisting of phenyl, or pyridino, wherein the substituents are selected from the group consisting of:

(a) $C_{0-6}CO_2R^{12}$, $C_{0-6}CON(*H)R^{12}$, $C_{0-6}NHSO_2R^{12}$, *trans*-$CH{=}CHCO_2R^{12}$, *trans*-$CH{=}CHCON(*H)R^{12}$, or cyclopropyl$CON(*H)R^{12}$ wherein R^{12} is C_{8-16} alkyl, bis-C_{4-16} alkyl (* no H), *N*-(methyl) C_{8-16} alkyl (* no H), C_{8-16} alkyloxyalkyl, C_{0-3} alkyl C_{7-10} perfluoroalkyl, C_{5-8} cycloalkyl, C_{2-11} alkylaryl, C_{1-5} alkylaryl C_{1-8} alkyl, aminoaryl, C_{0-4} alkyltetrahydrofurfuryl, C_{0-4} alkyldiphenylmethyl which the said alkyl group or said aryl group, are unsubstituted, mono- or disubstituted with a member selected from the group consisting of hydroxy, carboxy, halo, C_{1-6} alkyl and C_{1-6} alkyloxy, C_{1-6} cycloalkyloxy, C_1-C_4 alkyl aryl or C_1-C_4 alkoxy aryl, in which said aryl group is either unsubstituted, mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-4} alkyl, or C_{1-4} alkyloxy; or R^{10} can be N-Boc-piperidino, or N-carboethoxypiperidino;

And one of R^1, R^2, R^3, R^4 or R^5 must be selected from **Group III**:

Group III is defined as either:

(i) Hydrogen; or

(ii) Unsubstituted, mono or disubstituted C_{1-16} alkyl, C_{0-16} alkylamino,

amino C_{0-16} alkyl, C_{0-6} alkylcarboxyl or C_{0-6} alkyl carboxyl ester, C_{0-16} alkyloxyalkyl or C_{2-16} alkenyl wherein the substituents are independently selected from the group consisting of hydroxy, C_{1-8} alkyl, C_{1-8} alkyloxyalkyl, C_{1-8} alkylthioalkyl, phenyl-C_{1-8} alkylamino, C_{1-8} alkoxycarbonyl; or C_{0-6} carboxyl, triazole, 2,3-(methylenedioxy)benzyl; or

(iii) substituted or unsubstituted N or C-linked pyrrolidino, piperidino, piperidonyl, morpholino, piperazino, N-Boc-piperazino, N-C_{1-10} alkylpiperazino, N-C_{3-6} alkenylpiperazino, N-(C_{1-6} alkoxy C_{1-6} alkyl)piperazino, N-(C_{1-6} alkoxy C_{3-6} alkenyl)piperazino, N-(C_{1-6} alkylamino C_{1-6} alkyl)piperazino, N-(C_{1-6} alkylamino C_{3-6} alkenyl)piperazino, uracil or other purine or pyrimidine heterocycles, wherein the substituents are N or C-linked, and are independently selected from:

(a) substituted C_{1-16} alkyloxy, C_{3-16} alkenyloxy, substituted C_{3-16} alkynyloxy; or

(b) substituted C_{1-6} alkyl-amino, di(substituted C_{1-6} alkyl)amino; or

(c) CONHC_1-C_{16} alkyl, COOC_1-C_{16} alkyl, C_{0-11} alkylCO_2H, C_{0-11}NHC(O)NHR^{11}, C_{0-11}NHSO_2R^{11}, *trans*- CH=CHCO_2R^{11}, or *trans*- CH=CHCONHR^{11} wherein R^{11} is hydrogen, C_{1-16} alkyl, or C_{1-16} alkyl aryl, in which the said aryl group, is mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-6} alkyl and C_{1-6} alkyloxy, C_{1-6} cycloalkyloxy, or C_1-C_4 alkyl aryl or C_1-C_4 alkoxy aryl in which said aryl group is either unsubstituted, mono- or

disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-4} alkyl, C_{1-4} alkyloxy, and aryl; or

(i) either unsubstituted, mono-, di, or tri-substituted aryl, or C_0-C_{12} aryl, wherein the substituents are independently selected from;

(a) hydroxy, halo; or

(b) unsubstituted or substituted C_{0-3} alkyloxy C_{0-3} alkyl, C_{3-16} alkenyloxy, substituted C_{3-16} alkynyloxy, aryl; or

(c) mono or di-substituted C_{1-6} alkyl-amino, di(substituted C_{1-6} alkyl)amino; or

(d) $CONHC_1$-C_{16} alkyl, $COOC_1$-C_{16} alkyl, C_{0-11} alkylCO_2H, $C_{0-11}NHC(O)NHR^{11}$, $C_{0-11}NHSO_2R^{11}$, *trans*- $CH{=}CHCO_2R^{11}$, or *trans*- $CH{=}CHCONHR^{11}$ wherein R^{11} is hydrogen, C_{1-16} alkyl, or C_{1-16} alkyl aryl, in which the said aryl group, is mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-6} alkyl and C_{1-6} alkyloxy, C_{1-6} cycloalkyloxy, or C_1-C_4 alkyl aryl or C_1-C_4 alkoxy aryl in which said aryl group is either unsubstituted, mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-4} alkyl, C_{1-4} alkyloxy, and aryl.

(e) O- or C-linked hexose or furanose.

and one of R^1, R^2, R^3, R^4 or R^5 must be selected from **Group IV**:

Group IV is defined as either:

(i)hydrogen; or

(ii)substituted or unsubstituted C_{1-16} alkyl or C_{2-12} alkenyl wherein the substituents are independently selected from the group consisting of hydroxy, C_{1-6} alkyloxy, C_{1-6}alkylthio, C_{1-6} alkylamino, phenyl-C_{1-6} alkylamino, C_{1-6} alkoxycarbonyl; or

(iii) mono, di or tri-substituted aryl C_{0-4} alkyl or substituted C_{0-4} alkyl aryl, wherein the aryl group is selected from phenyl, imidazolyl, indolyl, furyl, thienyl or pyridyl in which the substituents are selected from:

(a)hydrogen; or

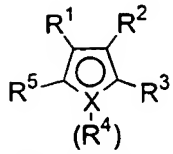
(b)hydroxy or halo

The remaining R group must be either unsubstituted or be equal to Hydrogen.

Case B: When two of R^1, R^2, R^3, or R^4 are selected from **Group I** (templates **1-6**), one of R^1, R^2, R^3, or R^4 must be selected from **Group II**, and one of R^1, R^2, R^3, or R^4 must be selected from **Group IV**. The remaining R groups must be either unsubstituted or be equal to Hydrogen; where **Groups I, II, III** and **IV** are defined above;

and the pharmaceutically acceptable salts and esters thereof.

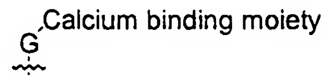
6. A compound having the structural Formula 3b:



X = N, S or O

Formula 3b

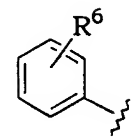
Where at least one and no more than two of R^1, R^2, R^3, R^4 or R^5 =



as defined in **Group 1**

Case A: When one of R^1, R^2, R^3, R^4, or $^*R^5$ (*in General Formula 3) is selected from **Group I** (template **7**):

Group I (template 7) is defined in Figure 2, Table 2, below:

Group I = 

where R^6 equals one of the following in Table 2:

Figure 2

Table 2

R^6 Type	Template	Atom or group					
		X	**Y**	**Z**	**R^7**	**R^8**	**R^9**
xvi	 **7a**	-	-	-	-	-	-

one of R^1, R^2, R^3, R^4 or $*R^5$ must be selected from **Group V**:

Group **V** is defined as one of the following:

(i) Unsubstituted, mono-, di-, or tri-substituted aryl-C_{0-11} alkyl wherein aryl is selected from the group consisting of phenyl, or pyridino, wherein the substituents are selected from the group consisting of:

(a) $C_{0-6}CO_2R^{12}$, $C_{0-6}CON(*H)R^{12}$, $C_{0-6}NHSO_2R^{12}$, *trans*-$CH{=}CHCO_2R^{12}$, *trans*-$CH{=}CHCON(*H)R^{12}$, or cyclopropylCON(*H)R^{12} wherein R^{12} is C_{8-16} alkyl, bis-C_{4-16} alkyl (* no H), *N*-(methyl) C_{8-16} alkyl (* no H), C_{8-16} alkyloxyalkyl, C_{0-3} alkyl C_{7-10} perfluoroalkyl, C_{5-8} cycloalkyl, C_{2-11} alkylaryl, C_{1-5} alkylaryl C_{1-8} alkyl, aminoaryl, C_{0-4} alkyltetrahydrofurfuryl, C_{0-4} alkyldiphenylmethyl which the said alkyl group or said aryl group, are unsubstituted, mono- or

disubstituted with a member selected from the group consisting of hydroxy, carboxy, halo, C_{1-6} alkyl and C_{1-6} alkyloxy, C_{1-6} cycloalkyloxy, C_1-C_4 alkyl.

and one of R^1, R^2, R^3, R^4 or $*R^5$ must be selected from **Group VI**.

Group VI is defined as one of the following:

(i) Hydrogen; or

(ii) either unsubstituted, mono-, di, or tri-substituted aryl, or C_0-C_{12} aryl, wherein the substituents are independently selected from;

(a) hydroxy, halo; or

(b) $CONHC_1$-C_{16} alkyl, $CONHC_{1-2}$ bis- C_{2-4} alkyl, $COOC_1$-C_{16} alkyl, C_{0-11} alkylCO_2H, $C_{0-11}NHC(O)NHR^{11}$, $C_{0-11}NHSO_2R^{11}$, *trans*-$CH{=}CHCO_2R^{11}$, or *trans*- $CH{=}CHCONHR^{11}$ wherein R^{11} is hydrogen, C_{1-16} alkyl, or C_{1-16} alkyl aryl, in which the said aryl groups are mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-6} alkyl and C_{1-6} alkyloxy, C_{1-6} cycloalkyloxy, or C_1-C_4 alkyl aryl or C_1-C_4 alkoxy aryl in which said aryl group is either unsubstituted, mono- or disubstituted with a member selected from the group consisting of hydroxy, halo, C_{1-4} alkyl, C_{1-4} alkyloxy, and aryl.

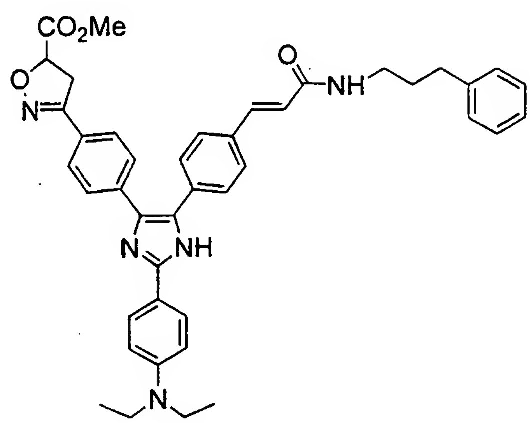
(c) O- or C-linked hexose or furanose.

The remaining R groups must be either unsubstituted or be equal to Hydrogen.

Case B: When two of R^1, R^2, R^3, R^4, or $*R^5$ (*in General Formula 3) are selected from **Group I** (template **7**), one of R^1, R^2, R^3, R^4 or $*R^5$ must be

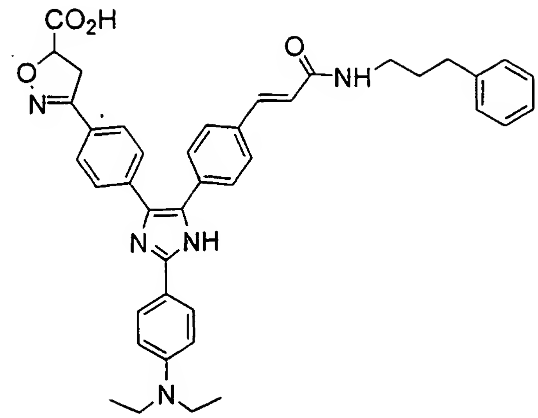
selected from **Group V**. The remaining R groups must be either unsubstituted or be equal to Hydrogen; where **Groups I, II, III, IV, V,** and **VI** are defined above.

7. A compound according to claim 1, by the name of 3-[4-(2-(4-Diethylamino-phenyl)-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester having the following structural formula:



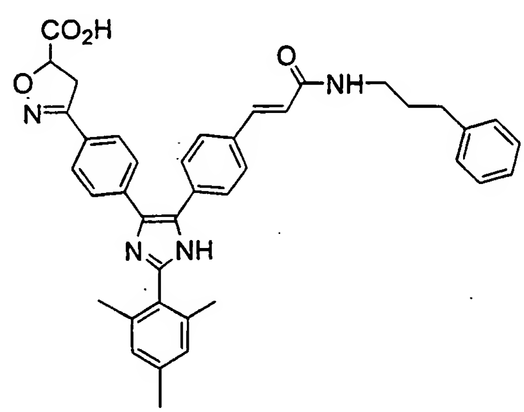
And the corresponding pharmaceutically acceptable salts thereof.

8. A compound according to claim 1, by the name of 3-[4-(2-(4-Diethylamino-phenyl)-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



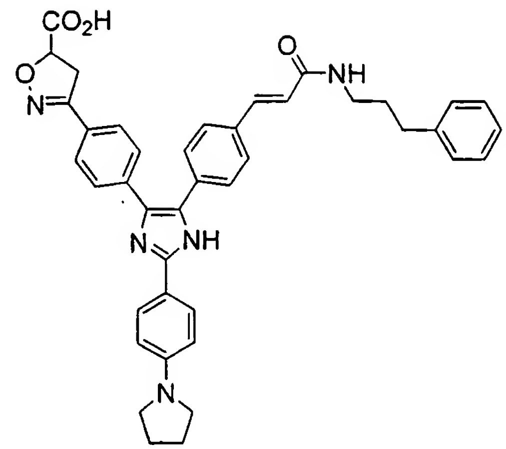
And the corresponding pharmaceutically acceptable salts and esters thereof.

9. A compound according to claim 1, by the name of 3-{4-[5-{4-[(E)-2-(3-Phenyl-propylcarbamoyl)-vinyl]-phenyl}-2-(2,4,6-trimethyl-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



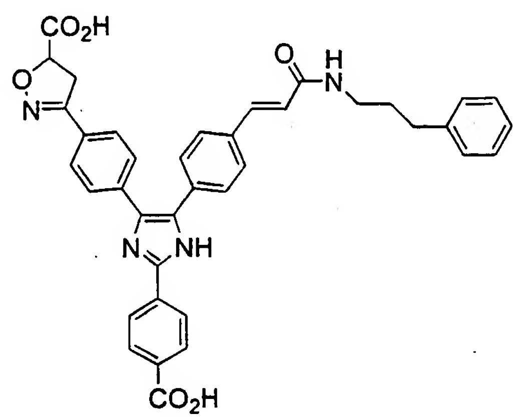
And the corresponding pharmaceutically acceptable salts and esters thereof.

10. A compound according to claim 1, by the name of 3-{4-[5-{4-[(E)-2-(3-Phenyl-propylcarbamoyl)-vinyl]-phenyl}-2-(4-pyrrolidin-1-yl-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



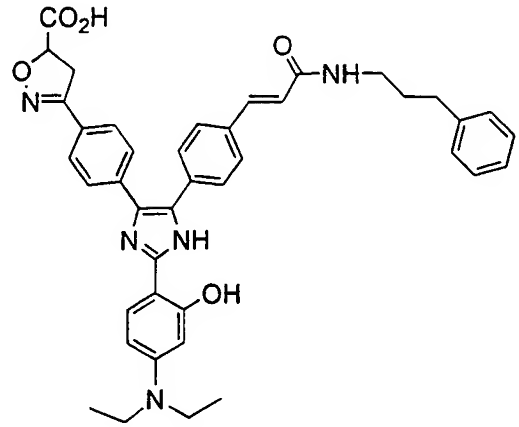
And the corresponding pharmaceutically acceptable salts and esters thereof.

11. A compound according to claim 1, by the name of 3-[4-(2-(4-Carboxy-phenyl)-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



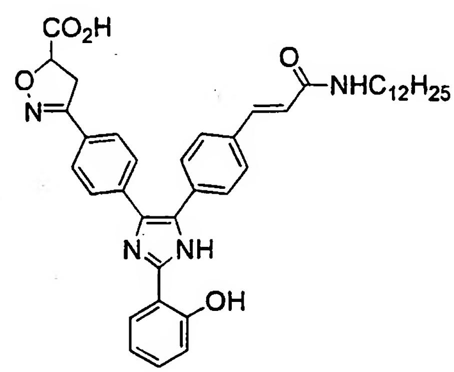
And the corresponding pharmaceutically acceptable salts and esters thereof.

12. A compound according to claim 1, by the name of 3-[4-(2-(4-Diethylamino-2-hydroxy-phenyl)-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



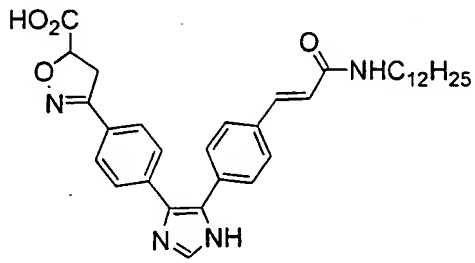
And the corresponding pharmaceutically acceptable salts and esters thereof.

13. A compound according to claim 1, by the name of 3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-(2-hydroxy-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



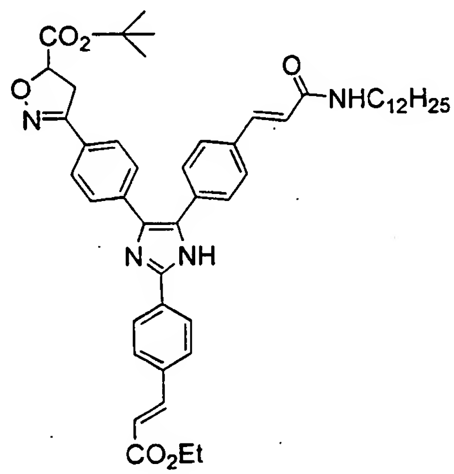
And the corresponding pharmaceutically acceptable salts and esters thereof.

14. A compound according to claim 1, by the name of 3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



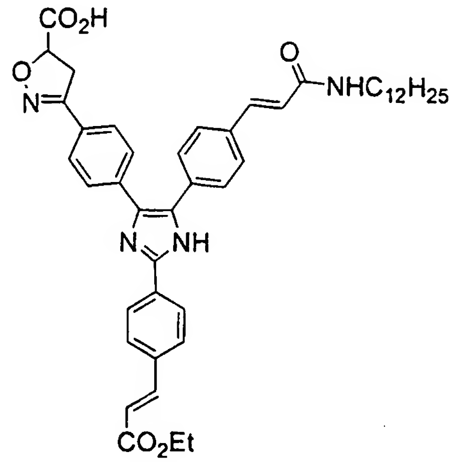
And the corresponding pharmaceutically acceptable salts and esters thereof.

15. A compound according to claim 1, by the name 3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester having the following structural formula:



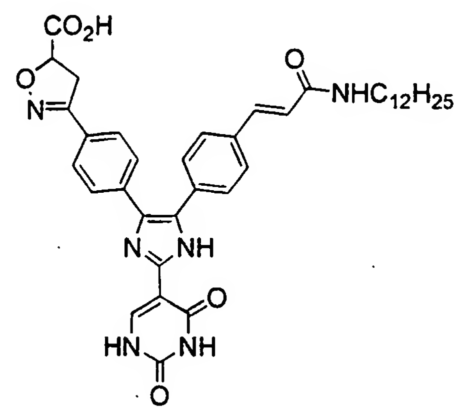
And the corresponding pharmaceutically acceptable salts thereof.

16. A compound according to claim 1, by the name of 3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



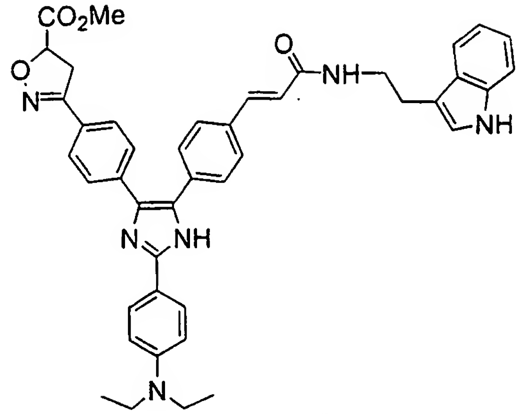
And the corresponding pharmaceutically acceptable salts and esters thereof.

17. A compound according to claim 1, by the name of 3-(4-{2-(2,4-Dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



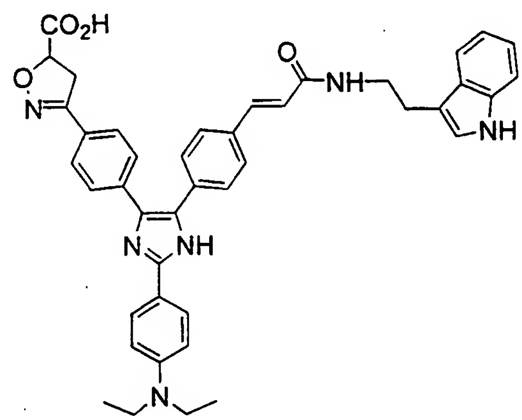
And the corresponding pharmaceutically acceptable salts and esters thereof.

18. A compound according to claim 1, by the name of 3-{4-[2-(4-Diethylamino-phenyl)-5-(4-{(E)-2-[2-(1*H*-indol-3-yl)-ethylcarbamoyl]-vinyl}-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester having the following structural formula:



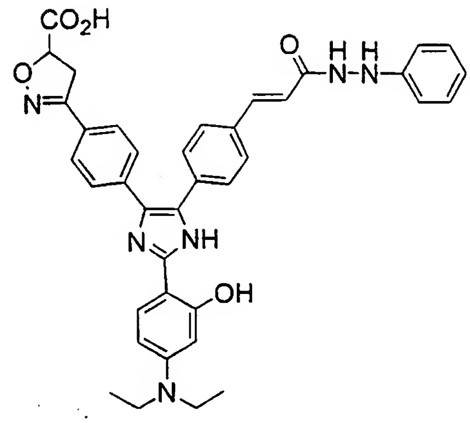
And the corresponding pharmaceutically acceptable salts and esters thereof.

19. A compound according to claim 1, by the name of 3-{4-[2-(4-Diethylamino-phenyl)-5-(4-{(E)-2-[2-(1*H*-indol-3-yl)-ethylcarbamoyl]-vinyl}-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



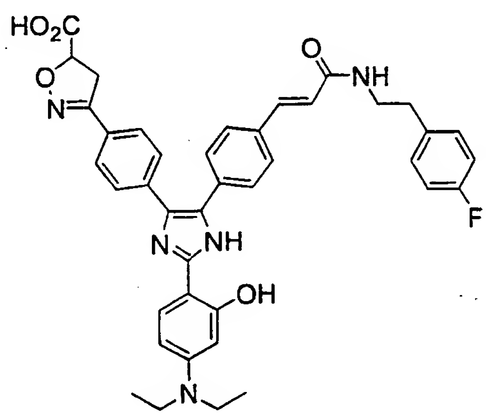
And the corresponding pharmaceutically acceptable salts and esters thereof.

20. A compound according to claim 1, by the name of 3-[4-(2-(4-Diethylamino-2-hydroxy-phenyl)-5-{4-[(E)-2-(*N*-phenyl-hydrazinocarbonyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



And the corresponding pharmaceutically acceptable salts and esters thereof.

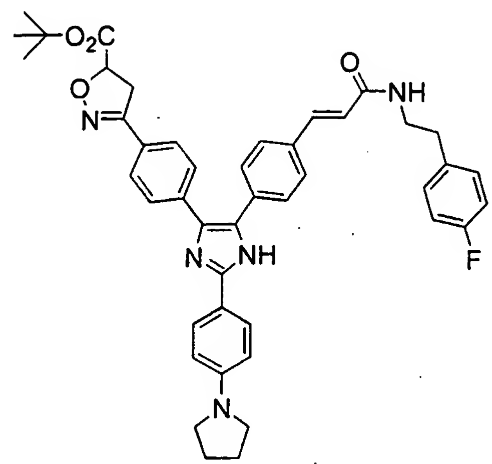
21. A compound according to claim 1, by the name of 3-{4-[2-(4-Diethylamino-2-hydroxy-phenyl)-5-(4-{(E)-2-[2-(4-fluoro-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



And the corresponding pharmaceutically acceptable salts and esters thereof.

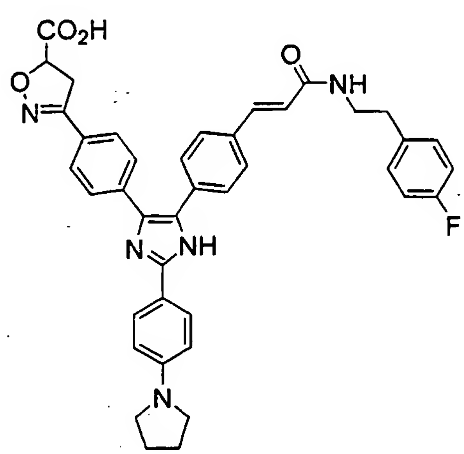
22. A compound according to claim 1, by the name of 3-{4-[5-(4-{(E)-2-[2-(4-Fluoro-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-2-(4-pyrrolidin-1-yl-

phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester having the following structural formula:



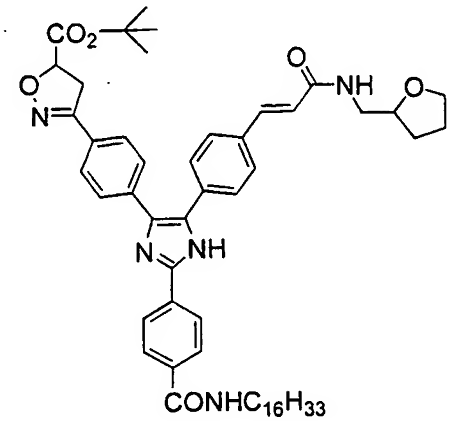
And the corresponding pharmaceutically acceptable salts and esters thereof.

23. A compound according to claim 1, by the name of 3-{4-[5-(4-{(E)-2-[2-(4-Fluoro-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-2-(4-pyrrolidin-1-yl-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



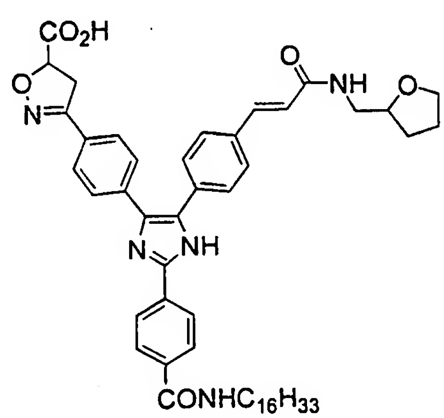
And the corresponding pharmaceutically acceptable salts and esters thereof.

24. A compound according to claim 1, by the name of 3-{4-[2-(4-Hexadecylcarbamoyl-phenyl)-5-(4-{(E)-2-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-vinyl}-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester having the following structural formula:



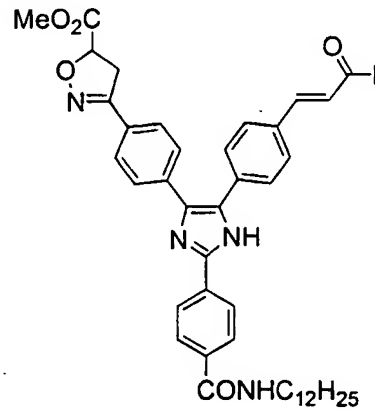
And the corresponding pharmaceutically acceptable salts thereof.

25. A compound according to claim 1, by the name of 3-{4-[2-(4-Hexadecylcarbamoyl-phenyl)-5-(4-{(E)-2-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-vinyl}-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



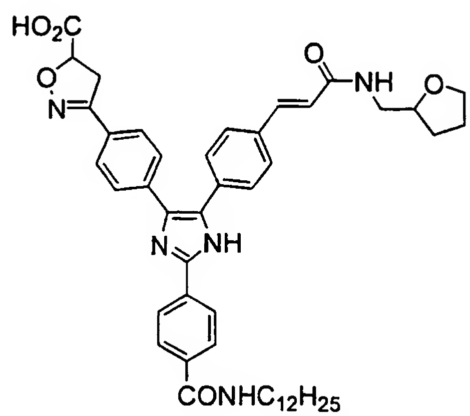
And the corresponding pharmaceutically acceptable salts and esters thereof.

26. A compound according to claim 1, by the name of 3-{4-[2-(4-Dodecylcarbamoyl-phenyl)-5-(4-{(E)-2-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-vinyl}-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester having the following structural formula:



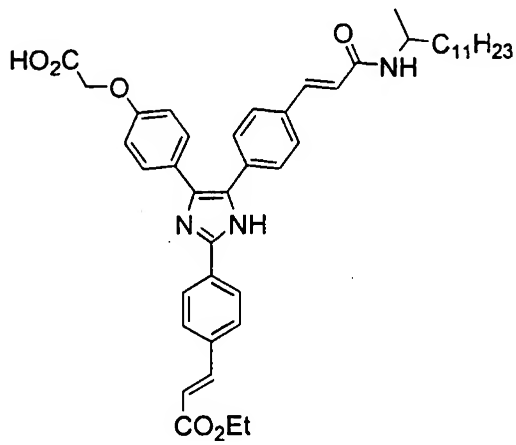
And the corresponding pharmaceutically acceptable salts thereof.

27. A compound according to claim 1, by the name of 3-{4-[2-(4-Dodecylcarbamoyl-phenyl)-5-(4-{(E)-2-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-vinyl}-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



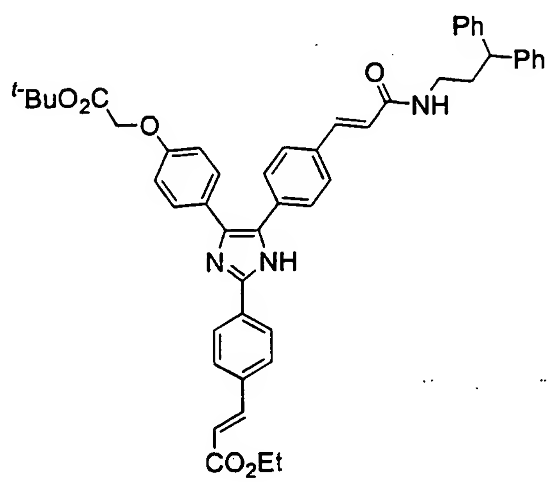
And the corresponding pharmaceutically acceptable salts and esters thereof.

28. A compound according to claim 1, by the name of [4-(2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-{4-[(E)-2-(1-methyl-dodecylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenoxy]-acetic acid having the following structural formula:



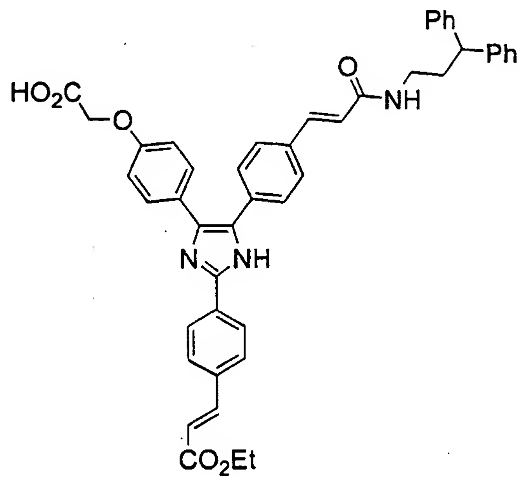
And the corresponding pharmaceutically acceptable salts and esters thereof.

29. A compound according to claim 1, by the name of (4-{5-{4-[(E)-2-(3,3-Diphenyl-propylcarbamoyl)-vinyl]-phenyl}-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenoxy)-acetic acid *tert*-butyl ester having the following structural formula:



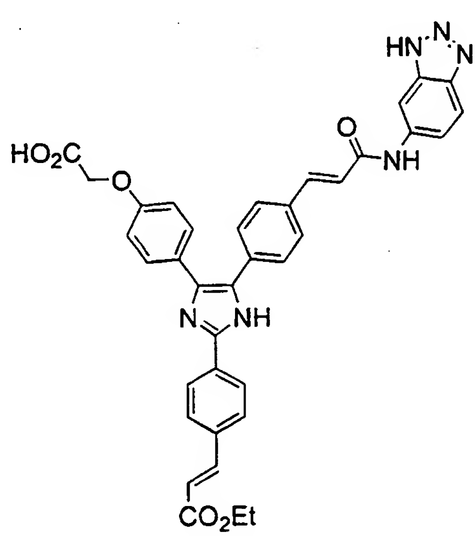
And the corresponding pharmaceutically acceptable salts thereof.

30. A compound according to claim 1, by the name of (4-{5-{4-[(E)-2-(3,3-Diphenyl-propylcarbamoyl)-vinyl]-phenyl}-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenoxy)-acetic acid having the following structural formula:



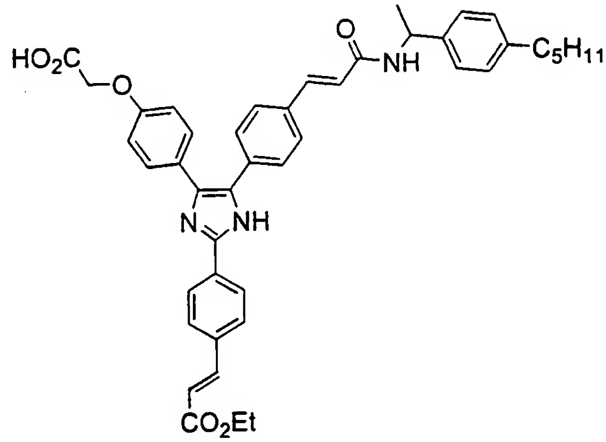
And the corresponding pharmaceutically acceptable salts and esters thereof.

31. A compound according to claim 1, by the name of (4-{5-{4-[(E)-2-(3*H*-Benzotriazol-5-ylcarbamoyl)-vinyl]-phenyl}-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenoxy)-acetic acid having the following structural formula:



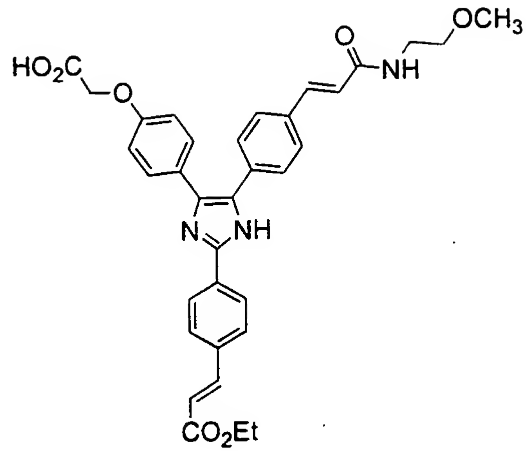
And the corresponding pharmaceutically acceptable salts and esters thereof.

32. A compound according to claim 1, by the name of {4-[2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-(4-{(E)-2-[1-(4-pentyl-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-1*H*-imidazol-4-yl]-phenoxy}-acetic acid having the following structural formula:



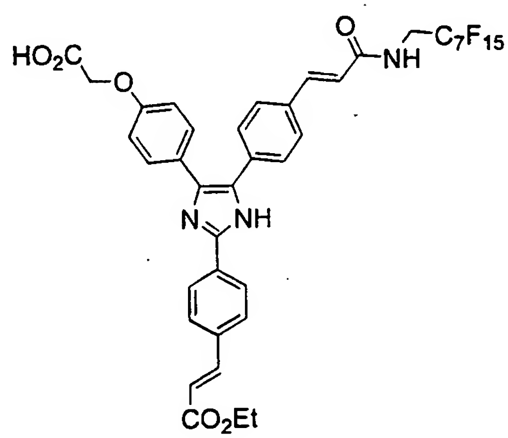
And the corresponding pharmaceutically acceptable salts and esters thereof.

33. A compound according to claim 1, by the name of [4-(2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-{4-[(E)-2-(2-methoxy-ethylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenoxy]-acetic acid having the following structural formula:



And the corresponding pharmaceutically acceptable salts and esters thereof.

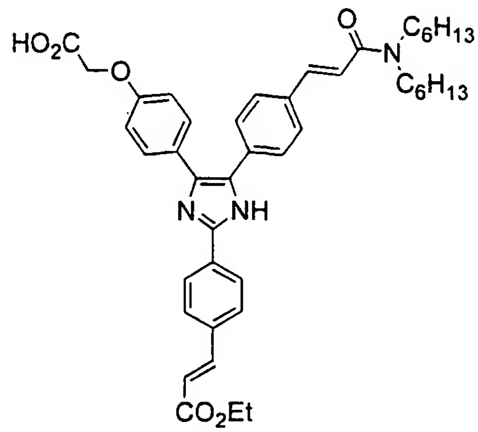
34. A compound according to claim 1, by the name of [4-(2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-{4-[(E)-2-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluoro-octylcarbamoyl)-vinyl]-phenyl}-1H-imidazol-4-yl)-phenoxy]-acetic acid having the following structural formula:



And the corresponding pharmaceutically acceptable salts and esters thereof.

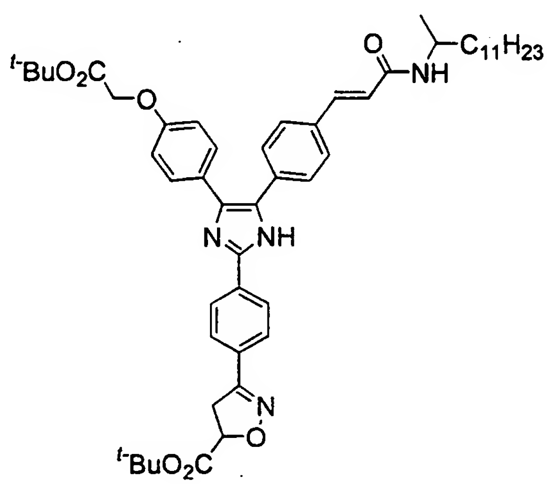
35. A compound according to claim 1, by the name of (E)-3-(4-{4-(4-Carboxymethoxy-phenyl)-5-[4-((E)-2-dihexylcarbamoyl-vinyl)-phenyl]-1*H*-

imidazol-2-yl}-phenyl)-acrylic acid ethyl ester having the following structural formula:



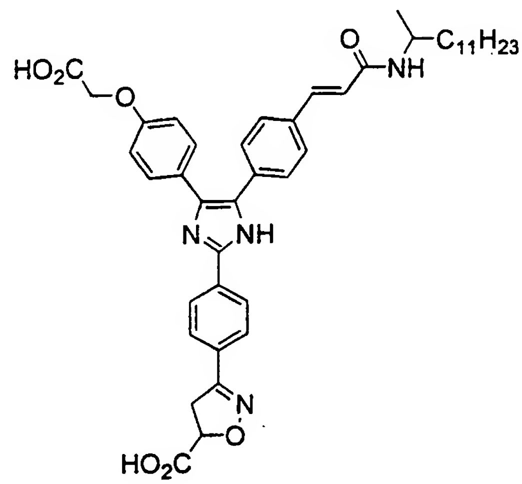
And the corresponding pharmaceutically acceptable salts and esters thereof.

36. A compound according to claim 1, by the name of 3-[4-(4-(4-*tert*-Butoxycarbonylmethoxy-phenyl)-5-{4-[(E)-2-(1-methyl-dodecylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester having the following structural formula:



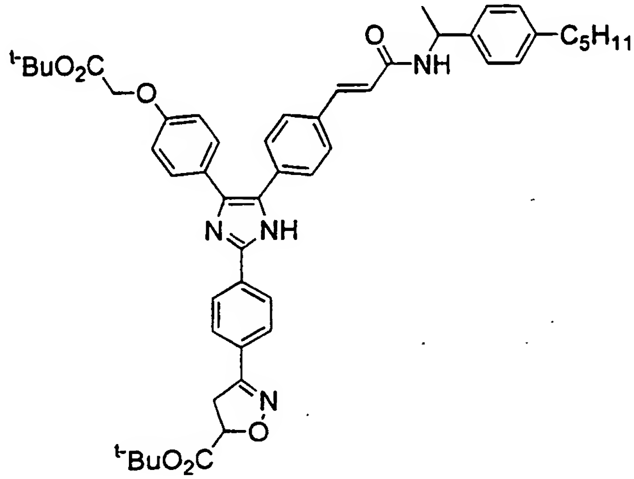
And the corresponding pharmaceutically acceptable salts thereof.

37. A compound according to claim 1, by the name of 3-[4-(4-(4-Carboxymethoxy-phenyl)-5-{4-[(E)-2-(1-methyl-dodecylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



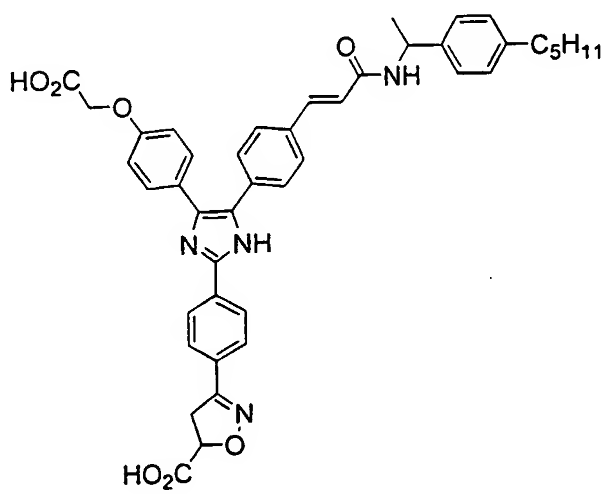
And the corresponding pharmaceutically acceptable salts and esters thereof.

38. A compound according to claim 1, by the name of 3-{4-[4-(4-*tert*-Butoxycarbonylmethoxy-phenyl)-5-(4-{(E)-2-[1-(4-pentyl-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-1*H*-imidazol-2-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester having the following structural formula:



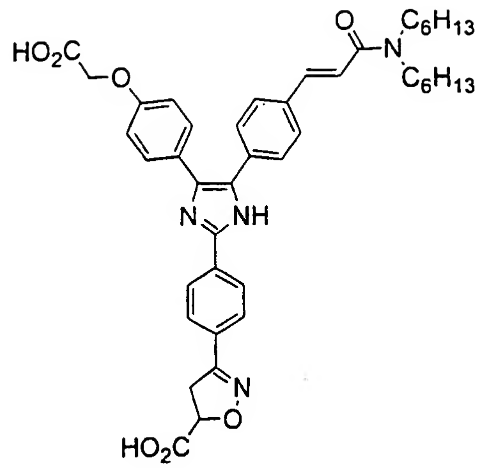
And the corresponding pharmaceutically acceptable salts thereof.

39. A compound according to claim 1, by the name of 3-{4-[4-(4-Carboxymethoxy-phenyl)-5-(4-{(E)-2-[1-(4-pentyl-phenyl)-ethylcarbamoyl]-vinyl}-phenyl)-1*H*-imidazol-2-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



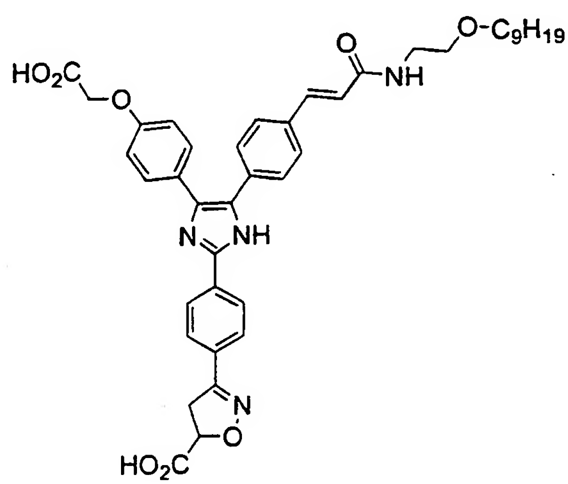
And the corresponding pharmaceutically acceptable salts and esters thereof.

40. A compound according to claim 1, by the name of 3-(4-{4-(4-carboxymethoxy-phenyl)-5-[4-((E)-2-dihexylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



And the corresponding pharmaceutically acceptable salts and esters thereof.

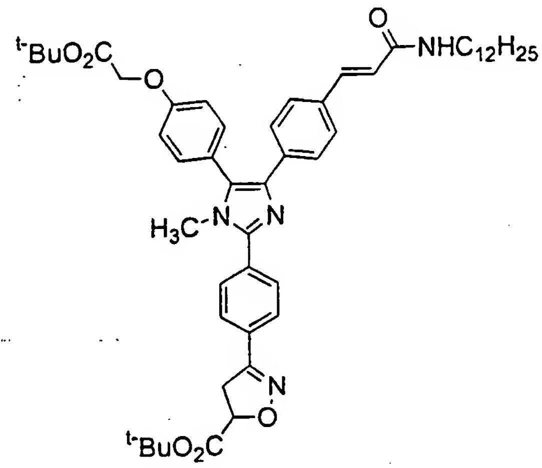
41. A compound according to claim 1, by the name of 3-[4-(4-(4-Carboxymethoxy-phenyl)-5-{4-[(E)-2-(2-nonyloxy-ethylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



And the corresponding pharmaceutically acceptable salts and esters thereof.

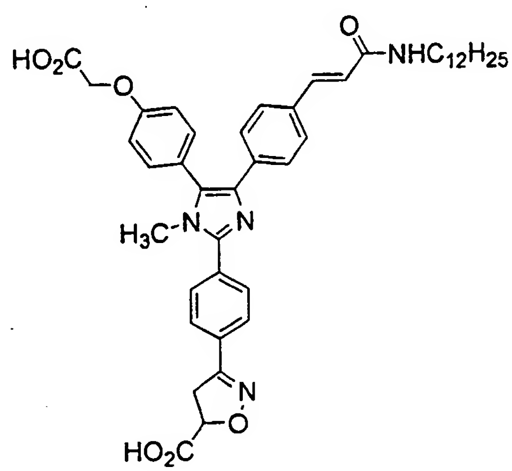
42. A compound according to claim 1, by the name of 3-(4-{5-(4-*tert*-Butoxycarbonylmethoxy-phenyl)-4-[4-((E)-2-dodecylcarbamoyl-vinyl)-

phenyl]-1-methyl-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester having the following structural formula:



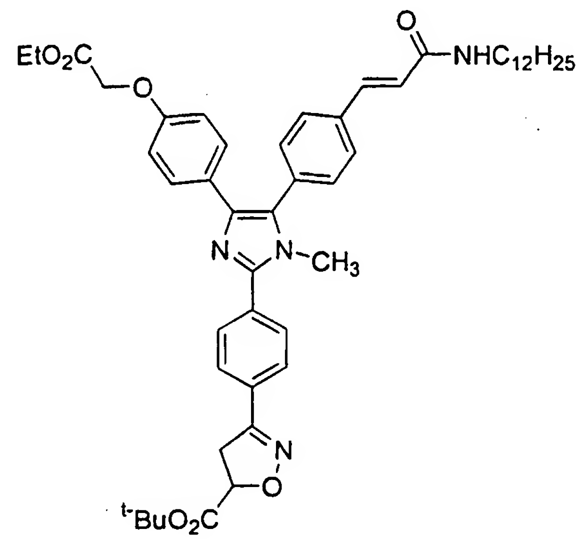
And the corresponding pharmaceutically acceptable salts thereof.

43. A compound according to claim 1, by the name of 3-(4-{5-(4-Carboxymethoxy-phenyl)-4-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1-methyl-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



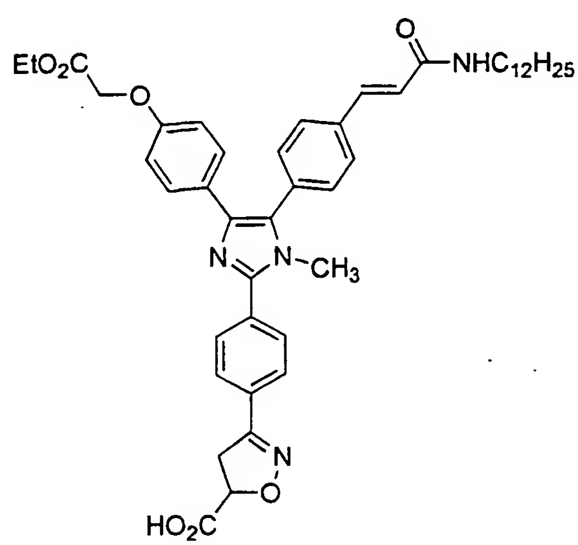
And the corresponding pharmaceutically acceptable salts and esters thereof.

44. A compound according to claim 1, by the name of 3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-(4-ethoxycarbonylmethoxy-phenyl)-1-methyl-1*H*-imidazol-2-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid *tert*-butyl ester having the following structural formula:



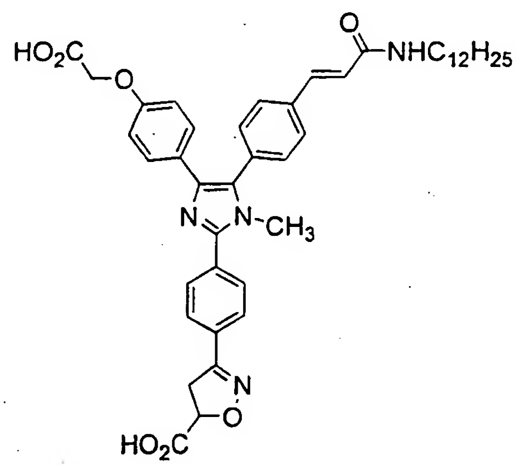
And the corresponding pharmaceutically acceptable salts thereof.

45. A compound according to claim 1, by the name of 3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-(4-ethoxycarbonylmethoxy-phenyl)-1-methyl-1*H*-imidazol-2-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



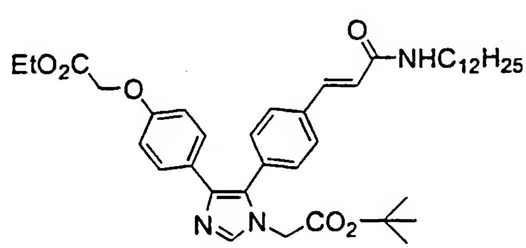
And the corresponding pharmaceutically acceptable salts and esters thereof.

46. A compound according to claim 1, by the name of 3-(4-{4-(4-Carboxymethoxy-phenyl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1-methyl-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



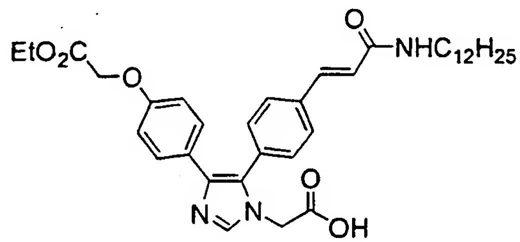
And the corresponding pharmaceutically acceptable salts and esters thereof.

47. A compound according to claim 1, by the name of [5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-(4-ethoxycarbonylmethoxy-phenyl)-imidazol-1-yl]-acetic acid *tert*-butyl ester having the following structural formula:



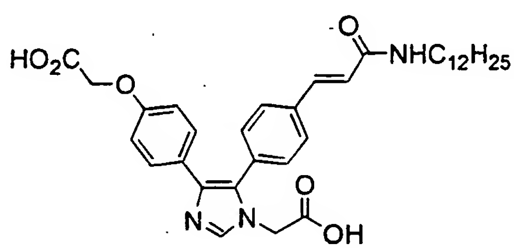
And the corresponding pharmaceutically acceptable salts thereof.

48. A compound according to claim 1, by the name of [5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-(4-ethoxycarbonylmethoxy-phenyl)-imidazol-1-yl]-acetic acid having the following structural formula:



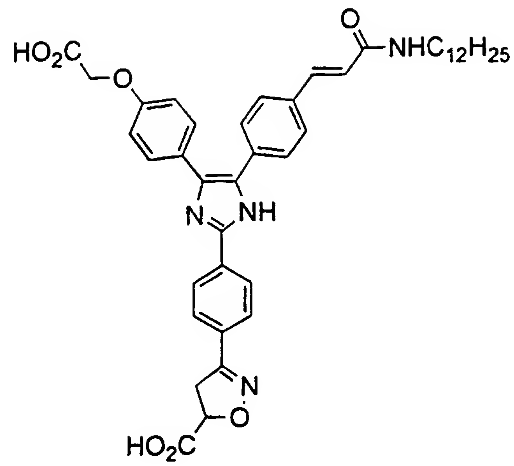
And the corresponding pharmaceutically acceptable salts and esters thereof.

49. A compound according to claim 1, by the name of {4-(4-Carboxymethoxy-phenyl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-imidazol-1-yl}-acetic acid having the following structural formula:



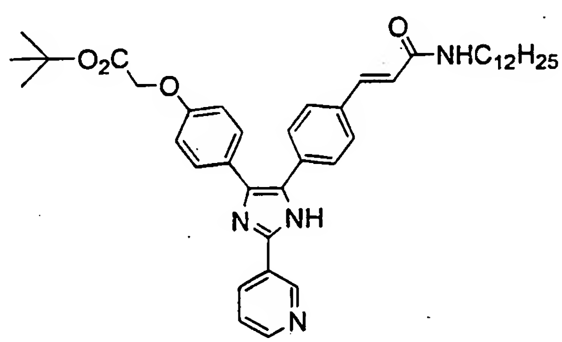
And the corresponding pharmaceutically acceptable salts and esters thereof.

50. A compound according to claim 1, by the name of 3-(4-{4-(4-Carboxymethoxy-phenyl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



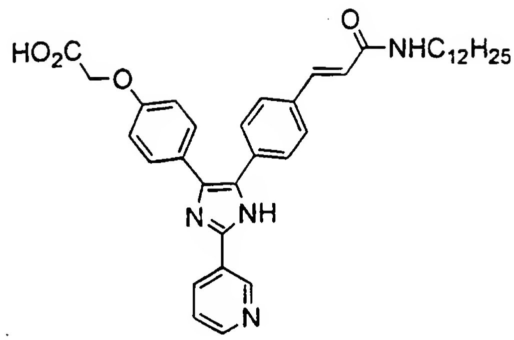
And the corresponding pharmaceutically acceptable salts and esters thereof.

51. A compound according to claim 1, by the name of {4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-pyridin-3-yl-1*H*-imidazol-4-yl}-phenoxy)-acetic acid *tert*-butyl ester having the following structural formula:



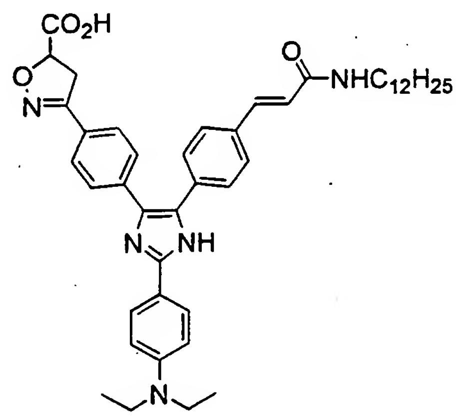
And the corresponding pharmaceutically acceptable salts thereof.

52. A compound according to claim 1, by the name of {4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-pyridin-3-yl-1*H*-imidazol-4-yl}-phenoxy)-acetic acid having the following structural formula:



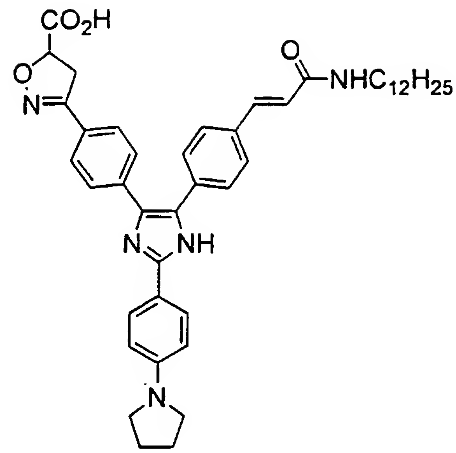
And the corresponding pharmaceutically acceptable salts and esters thereof.

53. A compound according to claim 1, by the name of 3-(4-{2-(4-Diethylamino-phenyl)-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



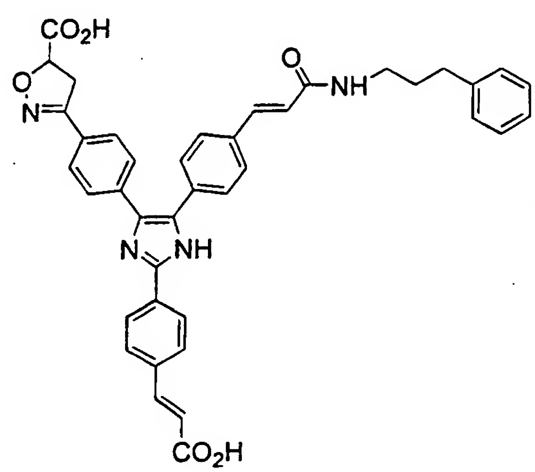
And the corresponding pharmaceutically acceptable salts and esters thereof.

54. A compound according to claim 1, by the name of 3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-(4-pyrrolidin-1-yl-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



And the corresponding pharmaceutically acceptable salts and esters thereof.

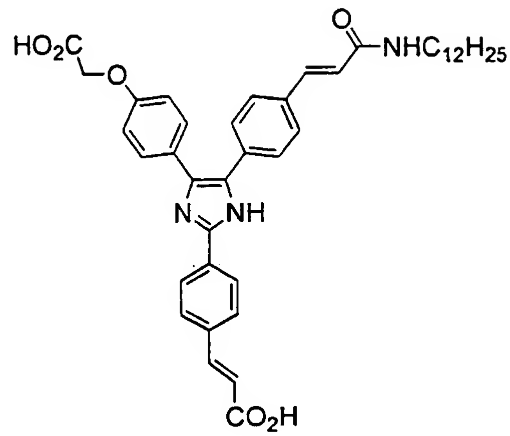
55. A compound according to claim 1, by the name of 3-[4-(2-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-{4-[(E)-2-(3-phenyl-propylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



And the corresponding pharmaceutically acceptable salts and esters thereof.

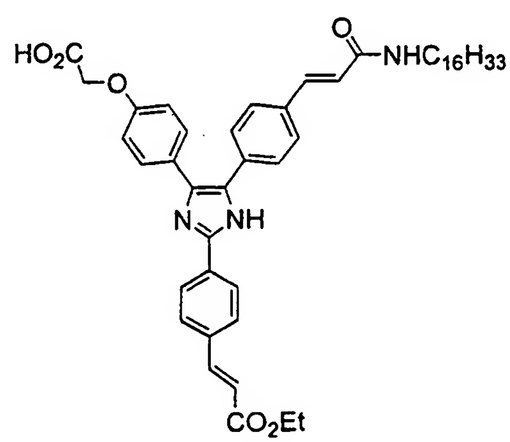
56. A compound according to claim 1, by the name of (4-{2-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-((E)-2-dodecylcarbamoyl-vinyl)-phenyl]-1*H*-

imidazol-4-yl}-phenoxy)-acetic acid having the following structural formula:



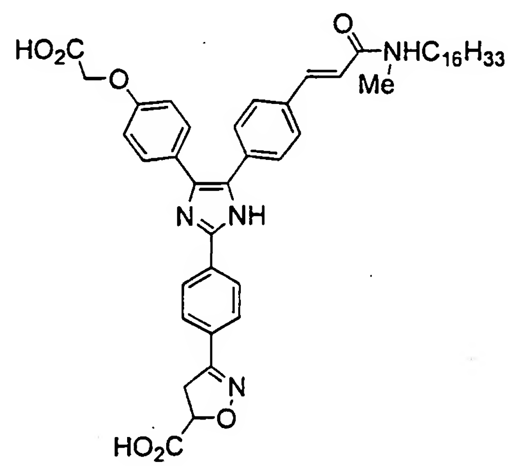
And the corresponding pharmaceutically acceptable salts and esters thereof.

57. A compound according to claim 1, by the name of {4-{5-[4-((E)-2-Hexadecylcarbamoyl-vinyl)-phenyl]-2-[4-((E)-2-ethoxycarbonyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenoxy)-acetic acid having the following structural formula:



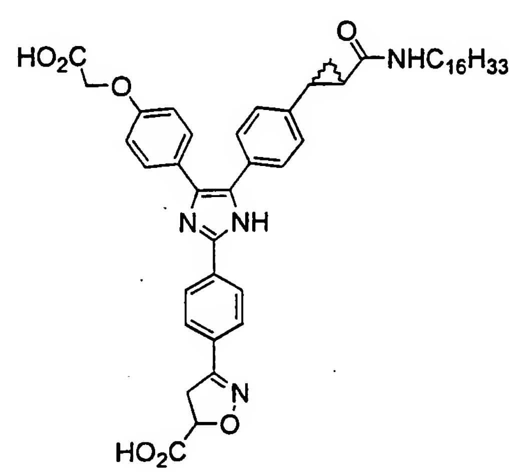
And the corresponding pharmaceutically acceptable salts and esters thereof.

58. A compound according to claim 1, by the name of 3-[4-(4-(4-Carboxymethoxy-phenyl)-5-{4-[(E)-2-(hexadecyl-methyl-carbamoyl)-vinyl]-phenyl}-1H-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



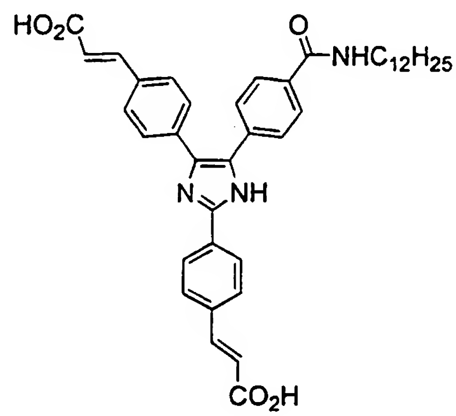
And the corresponding pharmaceutically acceptable salts and esters thereof.

59. A compound according to claim 1, by the name of 3-(4-{4-(4-Carboxymethoxy-phenyl)-5-[4-(2-hexadecylcarbamoyl-cyclopropyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



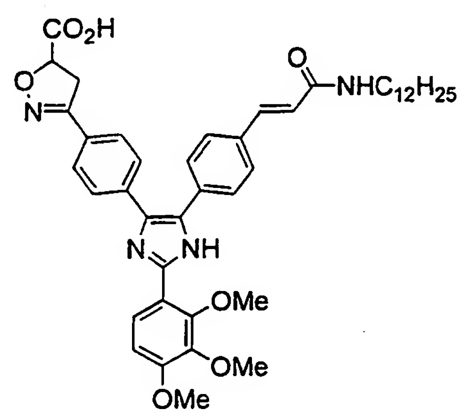
And the corresponding pharmaceutically acceptable salts and esters thereof.

60. A compound according to claim 2, by the name of (E)-3-{4-[4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-(4-dodecylcarbamoyl-phenyl)-1*H*-imidazol-2-yl]-phenyl}-acrylic acid having the following structural formula:



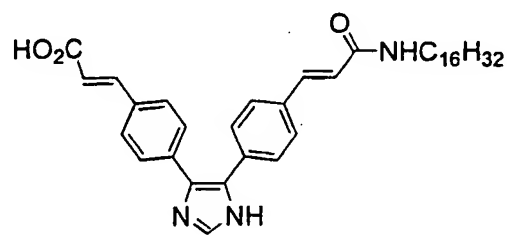
And the corresponding pharmaceutically acceptable salts and esters thereof.

61. A compound according to claim 1, by the name of 3-{4-[5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-2-(2,3,4-trimethoxy-phenyl)-1*H*-imidazol-4-yl]-phenyl}-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



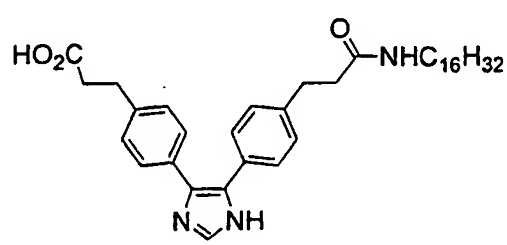
And the corresponding pharmaceutically acceptable salts and esters thereof.

62. A compound according to claim 2, by the name of (E)-3-(4-{5-[4-((E)-2-Hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-acrylic acid having the following structural formula:



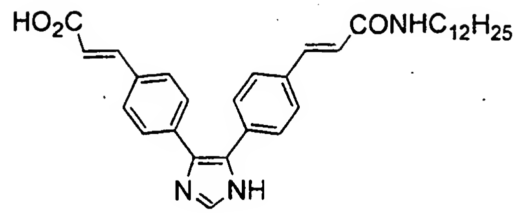
And the corresponding pharmaceutically acceptable salts and esters thereof.

63. A compound according to claim 1, by the name of 3-(4-{5-[4-(2-Hexadecylcarbamoyl-ethyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-propionic acid having the following structural formula:



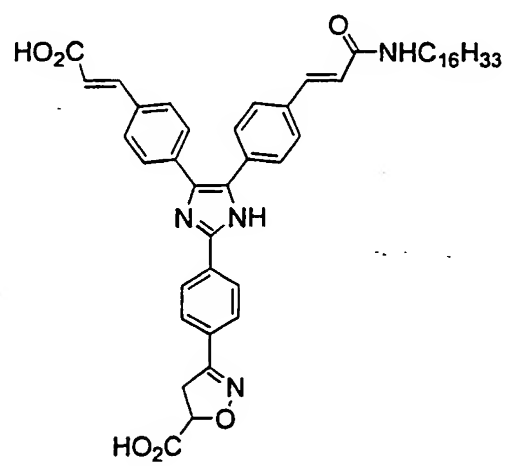
And the corresponding pharmaceutically acceptable salts and esters thereof.

64. A compound according to claim 2, by the name of (E)-3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-1H-imidazol-4-yl}-phenyl)-acrylic acid having the following structural formula:



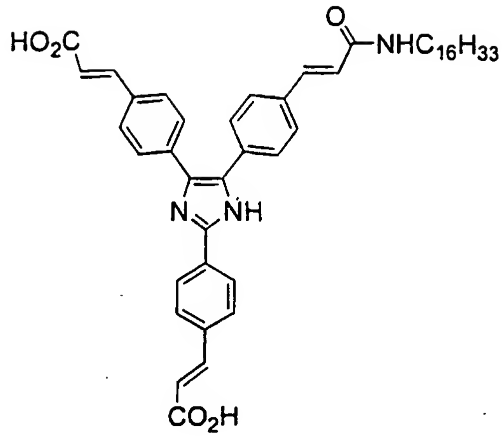
And the corresponding pharmaceutically acceptable salts and esters thereof.

65. A compound according to claim 1, by the name of 3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



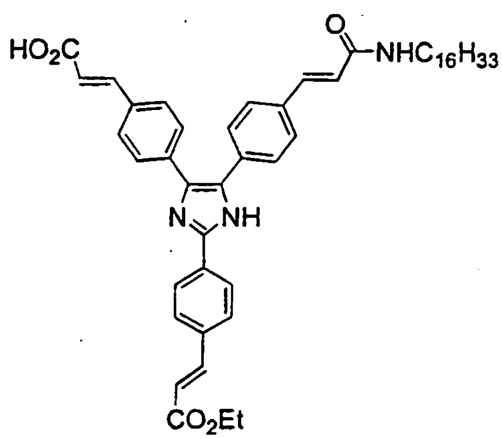
And the corresponding pharmaceutically acceptable salts and esters thereof.

66. A compound according to claim 2, by the name of (E)-3-(4-{2-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-acrylic acid having the following structural formula:



And the corresponding pharmaceutically acceptable salts and esters thereof.

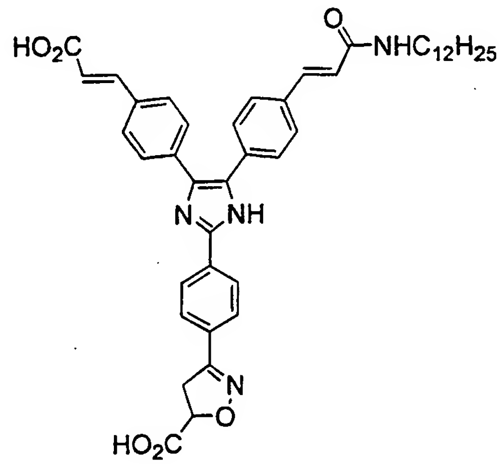
67. A compound according to claim 2, by the name of <u>(E)-3-(4-{2-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-acrylic acid</u> having the following structural formula:



And the corresponding pharmaceutically acceptable salts and esters thereof.

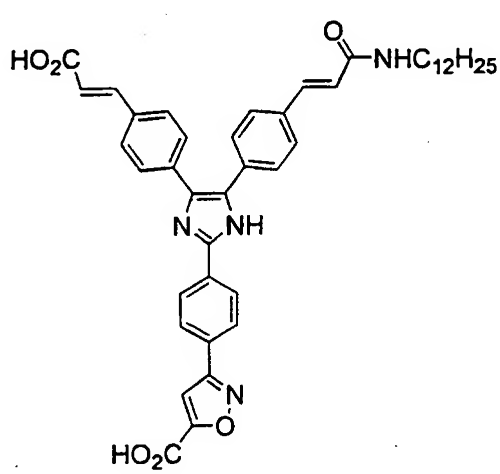
68. A compound according to claim 1, by the name of 3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-dodecylcarbamoyl-vinyl)-phenyl]-1*H*-

imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



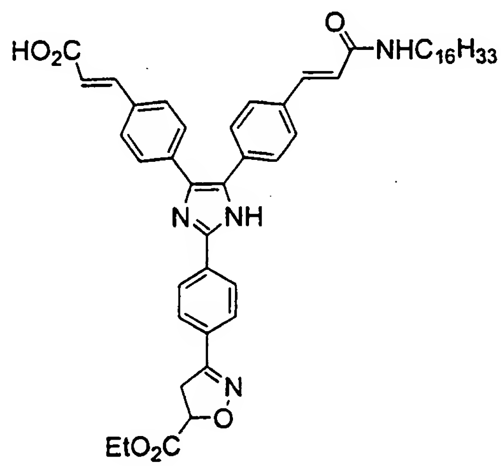
And the corresponding pharmaceutically acceptable salts and esters thereof.

69. A compound according to claim 1, by the name of 3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-dodecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-isoxazole-5-carboxylic acid having the following structural formula:



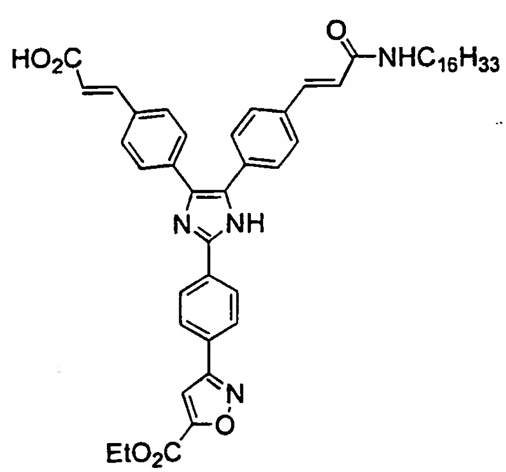
And the corresponding pharmaceutically acceptable salts and esters thereof.

70. A compound according to claim 1, by the name of 3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester having the following structural formula:



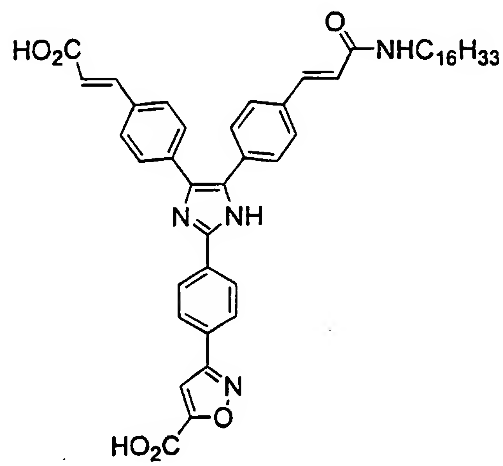
And the corresponding pharmaceutically acceptable salts and esters thereof.

71. A compound according to claim 1, by the name of 3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-isoxazole-5-carboxylic acid ethyl ester having the following structural formula:



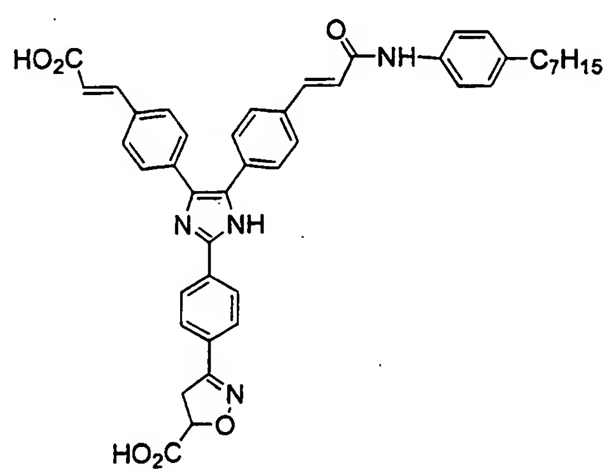
And the corresponding pharmaceutically acceptable salts and esters thereof.

72. A compound according to claim 1, by the name of 3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-isoxazole-5-carboxylic acid having the following structural formula:



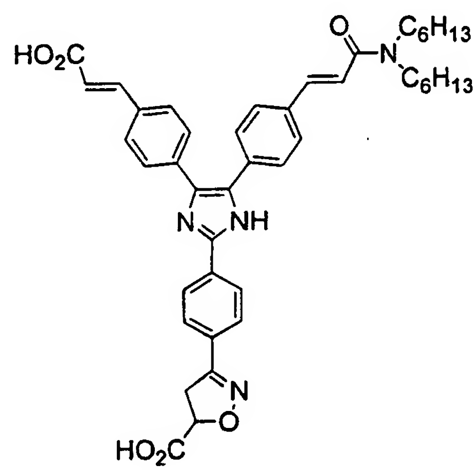
And the corresponding pharmaceutically acceptable salts and esters thereof.

73. A compound according to claim 1, by the name of 3-[4-(4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-{4-[2-(4-heptyl-phenylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



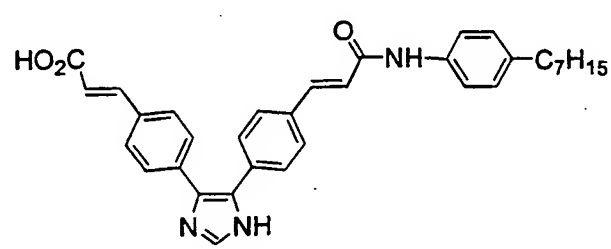
And the corresponding pharmaceutically acceptable salts and esters thereof.

74. A compound according to claim 1, by the name of 3-(4-{4-[4-((E)-2-Carboxy-vinyl)-phenyl]-5-[4-(2-dihexylcarbamoyl-vinyl)-phenyl]-1H-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



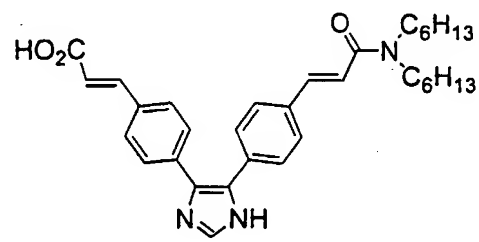
And the corresponding pharmaceutically acceptable salts and esters thereof.

75. A compound according to claim 2, by the name of (E)-3-[4-(5-{4-[(E)-2-(4-Heptyl-phenylcarbamoyl)-vinyl]-phenyl}-1*H*-imidazol-4-yl)-phenyl]-acrylic acid having the following structural formula:



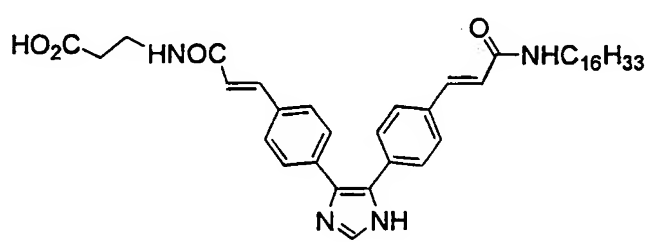
And the corresponding pharmaceutically acceptable salts and esters thereof.

76. A compound according to claim 2, by the name of (E)-3-(4-{5-[4-((E)-2-Dihexylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-acrylic acid having the following structural formula:



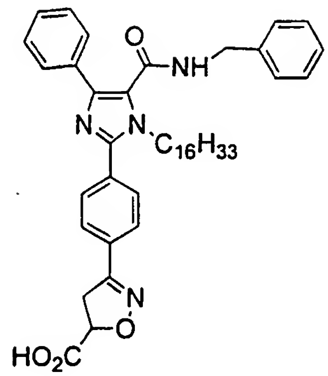
And the corresponding pharmaceutically acceptable salts and esters thereof.

77. A compound according to claim 1, by the name of 3-[3-(4-{5-[4-((E)-2-Hexadecylcarbamoyl-vinyl)-phenyl]-1*H*-imidazol-4-yl}-phenyl)-allanoylamino]-propionic acid having the following structural formula:



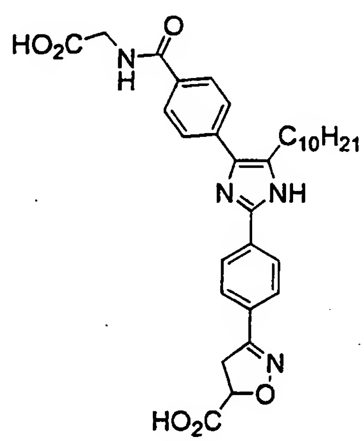
And the corresponding pharmaceutically acceptable salts and esters thereof.

78. A compound according to claim 1, by the name of 3-[4-(5-Benzylcarbamoyl-1-hexadecyl-4-phenyl-1*H*-imidazol-2-yl)-phenyl]-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



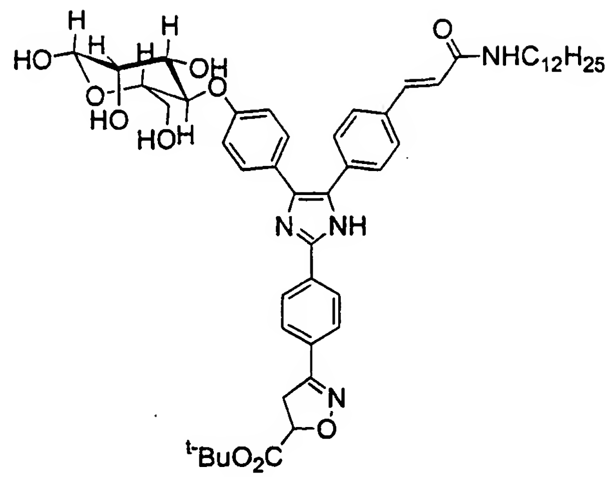
And the corresponding pharmaceutically acceptable salts and esters thereof.

79. A compound according to claim 1, by the name of 3-{4-{4-[4-(Carboxymethyl-carbamoyl)-phenyl]-5-decyl-1*H*-imidazol-2-yl}-phenyl)-4,5-dihydro-isoxazole-5-carboxylic acid having the following structural formula:



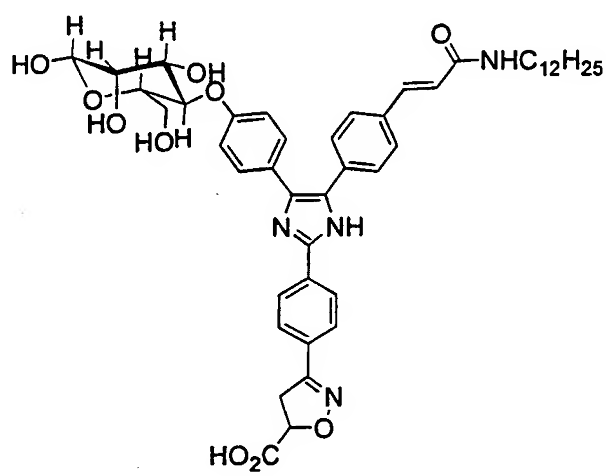
And the corresponding pharmaceutically acceptable salts thereof.

80. A compound according to claim 1, having the following structural formula:



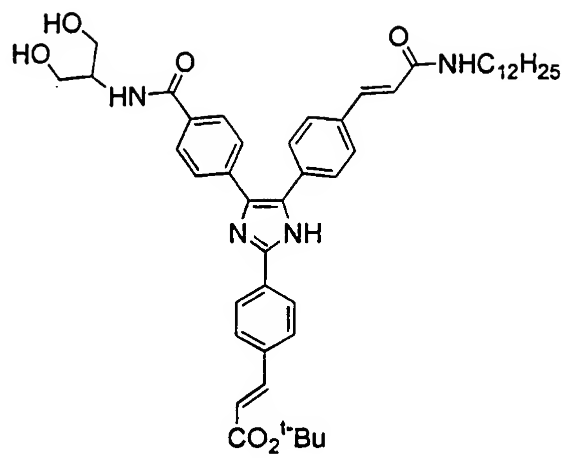
And the corresponding pharmaceutically acceptable salts thereof.

81. A compound according to claim 1, having the following structural formula:



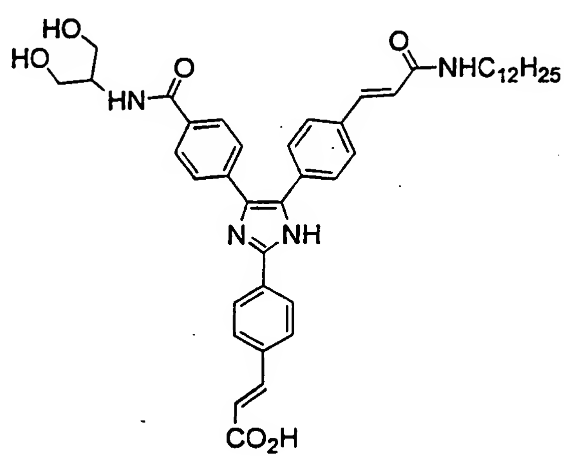
And the corresponding pharmaceutically acceptable salts and esters thereof.

82. A compound according to claim 2, by the name of (E)-3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-[4-(2-hydroxy-1-hydroxymethyl-ethylcarbamoyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-acrylic acid *tert*-butyl ester having the following structural formula:



And the corresponding pharmaceutically acceptable salts thereof.

83. A compound according to claim 2, by the name of (E)-3-(4-{5-[4-((E)-2-Dodecylcarbamoyl-vinyl)-phenyl]-4-[4-(2-hydroxy-1-hydroxymethyl-ethylcarbamoyl)-phenyl]-1*H*-imidazol-2-yl}-phenyl)-acrylic acid having the following structural formula:



And the corresponding pharmaceutically acceptable salts and esters thereof.

84. A method for treating human diseases involving P-, L- and E-selectin in a subject, which comprises the administration of an effective therapeutic amount of a compound selected from those defined in Claims

1-6, 43, 45, 50, 62, 65, 69-77 or the pharmaceutically acceptable salts and esters thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/28692

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/274, 341, 378, 396; 544/310; 546/270.4; 548/240, 334.1, 343.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,753,687 A (MJALLI et al.) 19 May, 1998, see the entire document.	1-84

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 FEBRUARY 2000	17 MAR 2000

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	TAOFIQ A SOLOLA
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

A61K 31/42, 497, 4172, 4412; C07D 213/02, 233/60, 401/04, 405/04, 413/04

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/274, 341, 378, 396; 544/310; 546/270.4; 548/240, 334.1, 343.5